Hanna-Maria Matinolli

NUTRITION AND EARLY LIFE PROGRAMMING OF HEALTH

FOCUS ON PRETERM BIRTH AND INFANT FEEDING IN RELATION TO ENERGY-BALANCE AND RELATED TRAITS IN ADULTHOOD
HANNA-MARIA MATINOLLI

NUTRITION AND EARLY LIFE PROGRAMMING OF HEALTH
Focus on preterm birth and infant feeding in relation to energy-balance and related traits in adulthood

Academic dissertation to be presented with the assent of the Doctoral Training Committee of Health and Biosciences of the University of Oulu for public defence in the Leena Palotie auditorium (101A) of the Faculty of Medicine (Aapistie 5 A), on 8 June 2018, at 12 noon

UNIVERSITY OF OULU, OULU 2018
Abstract

Increasing evidence suggests that early-life exposures influence the health and wellbeing in later life. Preterm birth (before 37 weeks of gestation) is associated with an increased risk of cardiometabolic disorders in later life. This risk may be partly mediated by nutrition along the course of life.

As a part of the Helsinki Study of Very Low Birth Weight Adults, the aim of the present work was to investigate the association between energy and macronutrient intake during the first weeks after preterm birth at very low birth weight (VLBW, birthweight < 1500g) and body composition and energy metabolism in adulthood (n=127). A further aim was to examine traits related to eating disorders and food and nutrient intake in young adults born early (<34 weeks of gestational age, n=191) and late (34-<37 weeks of gestational age, n=364) preterm and term-born controls (n=657) from the ESTER study and Arvo Ylppö Longitudinal study.

Relatively low neonatal energy and nutrient intakes during the first weeks of life of infants born at VLBW predicted body composition and energy metabolism in adulthood. When adjusted for sex, age, gestational age and birth-weight SD score every 1g/kg/day greater early protein intake was associated with 10.4% (95% CI 2.4, 19.1) higher lean body mass (LBM) and 8.5% (0.2, 17.0) higher resting energy expenditure (REE). The ratio of REE/LBM however was 5.5% (0.8, 10.0) lower. In addition, higher protein and energy intakes predicted lower energy intake per unit of LBM in young adults. These associations were only partly mediated by early growth.

Young women born early preterm reported on average healthier body image and fewer traits related to eating disorders when compared with term-born peers. However, their adherence to recommended eating guidelines was on average lower.

According to the results of present work, energy balance is partly programmed by relatively small variations in the amount of protein in the diet in infancy. Among young adults born preterm, focusing on primary prevention, such as dietary counseling, is suggested.

Keywords: body composition, body image, energy metabolism, food intake, infant feeding, premature infant, preterm birth
Matinolli, Hanna-Maria, Ravitsemus ja terveyden varhainen ohjelmoituminen. Ennenaikeisen syntymän ja varhaisen ravitsemuksen yhteys energia-aineenvaihduntaan ja siihen liittyviin piirteisiin aikuisiässä

Oulun yliopiston tutkijakoulu; Oulun yliopisto, Lääketieteellinen tiedekunta; Terveyden ja hyvinvoinnin laitos

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**Tiivistelmä**

Elämän varhaisvaiheet muokkaavat terveyttä ja hyvinvointia pitkällä aikavälillä. Ennenaikeisiin syntymään pyöristyneillä aikuisilla on todettu olevan suurempi riski sairastua sydän- ja verisuonitauteihin verrattuna täysiaikaisiin ikätovereihin. Ravitsemukseella, läpi elämänkaaren, on keskeinen rooli tuon riskin muokkaajana.

Tämän väitöskirjatuominnan tavoitteena oli selvittää osana Pikkuk-k-tutkimusta (n=127), miten pienipainoisina (syntymäpaino <1500g) syntyneiden keskosten elämän ensimmäisten viikkojen energia- ja ravintoaineiden saanti ennustaa kehonkoostumusta ja energiankulutusta sekä energian saantia aikuisiässä. Lisäksi tavoitteena oli tutkia ESTER- tai AYLS-kohorttitutkimuksiin osallistuneiden, hyvän (<34 raskausviikolla esineen, n=191) ja lievästi (34-37, n=364) keskosena syntyneiden ja täysiaikaisena syntyneiden (n=657) nuorten aikuisten syömishäiriöpiirteitä, kehonkuva sekä ruoan käyttöä ja ravintoaineiden saantia.

Suhteellisen matala elämän ensimmäisten viikkojen aikainen energian ja ravintoaineiden saanti ennustaa kehonkoostumusta ja energia-aineenvaihduntaa aikuisiässä. 1g/kg/päivä korkeampi proteiininsaanti oli yhteydessä 10,4% (95% luottamusväli 2,4; 19,1) suurempanaan ravitto, maan painoon sekä 8,5% (0,2; 17,0) korkeampaan lepoenergiankulutukseen aikuisiässä. Lepoenergiankulutus ravistontaan painoyksikköä kohden oli kuitenkin 5,5% (0,8; 10,0) matalampi enemmän proteiinia saaneilla keskosilla. Lisäksi korkeampi energian ja proteiininsaanti enemmän viikkojen aikana ennusti matalampaa energiansaantia painoyksikköä kohden aikuisiässä. Varhaisella kasvulla oli vain pieni rooli tämän yhteyden välittäjänä.

Nuorilla, hyvin ennenaikeisena (ennen 34. raskausviikkoa) syntyneillä, naisilla oli vähemmän syömishäiriöihin liittyviä piirteitä ja terveellisempi kehonkuva verrattuna heidän täysiaikaisena syntyneissä ikätovereihin. Arviotaessa heidän ruokavaliontaan, todettiin kuitenkin heidän syövän hieman epäterveellisemmin ikätovereihin verrattuna.

Tämän väitöskirjaturvahimpunen tulosten valossa varhainen puuttuminen keskosena syntyneiden lisääntyneeseen sydän- ja verisuonitauteihin on mahdollista kiinnittää huomiota varhaiseen ravitsemukseen ja varhaisen aikuisiän elintapaohjaukseen, etenkin ravitsemukseen liittyen.

**Asiassat:** energiametabolia, energiankulutus, energiansaanti, kehonkoostumus, keskoseet, ruokavalio, syömishäiriöt, varhainen ravitsemus
To my family
Acknowledgements

This work was initiated in 2011 in Oulu and finalized in 2018 in Helsinki and Paimio. During these years I have got to know numerous amazing people and learned a lot not only about science, but also about myself and what is important in life.

The work was mainly carried out at the National Institute for Health and Welfare (THL). I want to express my gratitude to the former and current directors of THL, Professors Pekka Puska and Juhani Eskola for providing the research facilities. Special thanks also go to the former and current heads of The Public Health Promotion Unit, Docent Jaana Lindström and Professor Markku Peltonen.

I have had two absolutely amazing supervisors. My main supervisor, Docent Eero Kajantie; you have believed in me, encouraged me to go forward and learn new things in totally new areas of research. In so many ways you have helped me to build the scientist inside me, even though you have always allowed me freedom and space to do things independently. Your experience as a multitalented scientist is truly inspirational. My other supervisor Docent Satu Männistö; I am deeply grateful for your wise and always efficient and productive advice. Thank you for keeping me on track. Thank you also for nice and warm conversations about other things important in life besides science. I also warmly want to acknowledge the director of the Institute of Health Sciences in Oulu, Professor Sirkka Keinänen-Kiukaanniemi for agreeing to be my degree supervisor.

I want to warmly thank the follow-up group connected with my work; Docent Tuija Tammelin from Likes and Professor Helvi Kyngäs, and Juha Auvinen, MD, PhD, from the University of Oulu. Tuija and Juha, you have given me practical advice and mental support when I have needed it; I am truly grateful. Helvi, you deserve a special thank you as you are the person who first introduced me to research during my Master’s studies. The joy of doing science comes from you. I am indebted to Docent Kirsi Laitinen and Docent Samuli Rautava from the University of Turku for their willingness to review the manuscript of my thesis. The wise advice and comments given by my pre-examiners has been a great help during the final stages of this process. Nick Bolton is thanked for careful editing of the English language. I am honoured and grateful to Professor Hazel Inskip for accepting the invitation to be my opponent. It is a privilege to have such an experienced and inspirational opponent.

The data used in this thesis came from three different cohort studies, the Helsinki Study of Very Low Birth Weight Adults, the ESTER study and the Arvo
Ylppö Longitudinal Study. Without the young adults who took part in these studies, this thesis would not have been possible. This is why I want to sincerely thank each and every one of them. I want to express my deepest gratitude to the professionals who have worked with these cohorts for years and at the same time paved the way for life-course epidemiology in Finland. Professors Johan Eriksson, Marjo-Riitta Järvelin, Katri Rääkkönen and Docents Anna-Liisa Järvenpää, Sture Andersson, Marja Vääräsmäki and Aulikki Lano are warmly acknowledged. The people who have been working on these cohort studies deserve great and sincere thanks. I sincerely want to thank all my co-authors: Petteri Hovi, Marika Sipola-Leppänen, Marjaana Tikanmäki, Dieter Wolke, Kati Heinonen, Marius Lahti, Jari Lahti, Esko Levälahti, Karoliina Wehkalampi, Nina Kaseva, Katri Hemiö, Patricia Pelufo Silveira, Outi Mäkitie and Timo Vartia. I have received many inspiring comments and ideas from you all that have been a great help in bringing the results of the present work alive.

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Lastly, my warmest thanks belong to you, Heikki and our wonderful children Jalmari and Anna. Heikki, thank you for always being there for me – I would not be here without you. The past years have been extremely busy with moving, building a house, raising kids and work. We made it! Jalmari and Anna, you bring the greatest happiness to my life. I love you more than anything!

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Paimio, March 2018

Hanna-Maria Matinolli
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AGA</td>
<td>Appropriate for gestational age</td>
</tr>
<tr>
<td>AN</td>
<td>Anorexia nervosa</td>
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<tr>
<td>BIA</td>
<td>Bioelectrical impedance analysis</td>
</tr>
<tr>
<td>BN</td>
<td>Bulimia nervosa</td>
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<tr>
<td>CI</td>
<td>Confidence interval</td>
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<tr>
<td>DOHaD</td>
<td>Developmental origins of health and disease</td>
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<tr>
<td>DXA</td>
<td>Dual energy X-ray absorptiometry</td>
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<tr>
<td>ED</td>
<td>Eating disorder</td>
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<td>EDI-2</td>
<td>Eating Disorder Inventory-2</td>
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<tr>
<td>FFQ</td>
<td>Food frequency questionnaire</td>
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<tr>
<td>FMBR</td>
<td>Finnish Medical Birth Register</td>
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<tr>
<td>GA</td>
<td>Gestational age</td>
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<tr>
<td>HeSVA</td>
<td>the Helsinki Study of Very Low Birth Weight Adults</td>
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<tr>
<td>IUGR</td>
<td>Intrauterine growth restriction</td>
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<tr>
<td>LBM</td>
<td>Lean body mass</td>
</tr>
<tr>
<td>LBW</td>
<td>Low birth weight</td>
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<tr>
<td>MET</td>
<td>Metabolic equivalent (of Task)</td>
</tr>
<tr>
<td>NICU</td>
<td>Neonatal intensive care unit</td>
</tr>
<tr>
<td>NFBC</td>
<td>Northern Finland Birth Cohort</td>
</tr>
<tr>
<td>RDI</td>
<td>Recommended diet index</td>
</tr>
<tr>
<td>REE</td>
<td>Resting energy expenditure</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SGA</td>
<td>Small for gestational age</td>
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<tr>
<td>VLBW</td>
<td>Very low birth weight</td>
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<td>VPT</td>
<td>Very preterm</td>
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</table>
List of original publications

This thesis is based on the following publications, which are referred to throughout the text by their Roman numerals (I-IV):


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1 Introduction

Compelling evidence exists of a link between *in utero* and early childhood environmental factors, and later health. The phenomenon linking early-life exposures to the risk of developing certain diseases, (in particular cardiometabolic diseases) in adulthood is now known as the “developmental origins of health and disease” (DOHaD) hypothesis (Barker, 2004). As obesity and related metabolic disorders are now major health problems across the globe (World Health Organization, 2014), it is vital to study the factors underlying them. It is commonly accepted that genetics and lifestyle have important parts to play. However, increasing evidence suggests that early-life exposures also influence the occurrence of these disorders. A large number of experimental animal studies has now demonstrated how materno-fetal and infant nutrition are associated with metabolic health in later life (reviewed in Langley-Evans, 2015). However, human evidence is limited and the association between early life factors and food and nutrient intake in adulthood is less well studied.

Preterm birth is defined as childbirth occurring before 37 full weeks of pregnancy (Blencowe *et al*., 2012). In Finland, 6% of all newborns were born prematurely in 2016 (THL, 2017). Together with the rising number of preterm births worldwide, advances in obstetric care and neonatal intensive care allow more preterm infants to survive into adulthood (Blencowe *et al*., 2012). Past studies have shown enhancement of cardiometabolic risk factors in those born preterm (Sipola-Leppänen & Kajantie, 2015). In addition, early nutritional management of preterm infants is associated with health and wellbeing throughout life (Harding, Cormack, Alexander, Alsweiler, & Bloomfield, 2017). Nutrition, especially increased consumption of energy-dense foods, is one of the most important factors behind the rising obesity epidemic (Swinburn, Caterson, Seidell, & James, 2004). Optimizing lifestyle, including dietary intake, is a way to reduce the adverse health effects of preterm birth.

The focus of this thesis, was firstly, to examine the associations between nutrition during the early weeks of life and body composition and energy metabolism in young adults born preterm with very low birth weight (VLBW, <1500g). Secondly, the focus was on assessing traits related to eating disorders and food and nutrient intake in young adults born preterm. The overarching hypothesis in this doctoral thesis was that food and nutrient intake, from early infancy to adulthood, and body image in adulthood have key roles in mediating and modifying...
the previously shown associations between preterm birth and adverse metabolic health in adult life.
2 Review of the literature

This thesis is focused on early programming of health, with a particular focus on preterm birth and nutrition in early life and at an adult age. The literature review will first address the theory behind the thesis, developmental origins of health and disease and the concept of programming. Preterm birth and its epidemiology will be addressed after, as well as past studies in the field of nutritional programming.

2.1 Developmental origins of health and disease

During the last few decades the scientific literature has well recognized the role of the early-life environment in contributing to health and disease in later life. The theory indicating that fetal and early-life experiences result in long-lasting alterations in health was first proposed by David Barker and colleagues in the late 1980’s (Barker, Osmond, Winter, Margetts, & Simmonds, 1989) although there have also been some historical precedents for it, as reviewed by McCance as early as in 1962, Dubois and colleagues in 1966, and Forsdahl in 1977 (McCance, 1962; Dubois, Savage, Dwayne, Schaedler, & Russell, 1966; Forsdahl, 1977).

Studies by Barker and his colleagues began in the 1970’s with epidemiological research on geographical variations of disease in England and Wales, as they found an association between the highest rates of neonatal deaths in 1910 and the highest prevalence of cardiovascular diseases in the same geographical area. This association was shown to be independent of postnatal factors. (Barker, 1988) They also found that in 5654 men from Hertfordshire, UK, that those with the lowest birth weights had the highest death rates from cardiovascular disease (Barker, Winter, Osmond, Margetts, & Simmonds, 1989). Studies by Barker and colleagues were followed by studies on the Helsinki Birth cohort (Forsen, Eriksson, Tuomilehto, Osmond, & Barker, 1999) and others (Martyn, Gale, Jespersen, & Sherriff, 1998) showing a link between lower birth weight and a higher risk of death from cardiovascular diseases independent of confounding factors such as socioeconomic status. The theory was first named the “thrifty phenotype hypothesis” or “small-baby-syndrome”. Later the field of research was named “The Fetal Origins of Adult Disease” and as the study of early-influencing factors widened to include exposures such as early nutrition, early toxin exposure and early social environment it was expanded to “Developmental origins of health and disease, DOHaD” in the later 1990’s.
2.1.1 The concept of programming

During the period of rapid growth and development, the fetus or newborn neonate is highly susceptible to alterations in the maternal or early postnatal environment. The term “programming”, first introduced by Alan Lucas (Lucas, 1991), refers to the process in which certain stimuli during a critical phase of development leads the organism to adapt to environmental events so that the adaptation results in permanent changes in future health and wellbeing. It is suggested that cells and tissues have their own time window during which they have “plasticity” and are responsive to the environment. Exposure to an adverse environment may affect the process of cell proliferation or differentiation, affect fetal growth and consequently have long-lasting effects on the individual’s health (Gluckman, Hanson, & Low, 2011; Langley-Evans, 2015).

The ability to program the functionality of cells and tissues is considered beneficial for an individual or an organism. However, it may also have damaging effects. As the human life span is long and especially because the effects of programming of human metabolic function are not seen until diseases arise in older age, animal models have been essential in providing insights to the possible mechanisms of programming. Animal models, including alteration of nutrition during different stages of gestation and postnatal life, have guided recent research via results suggesting that the timing of the adverse fetal events is crucial in finding the programming effects in postnatal life (Gugusheff, Ong, & Muhlhausler, 2015).

Inadequate early nutrition has been shown to affect the propensity to develop obesity in later life. In the thrifty phenotype hypothesis it was proposed that poor nutrition during early life programs tissue and organ functions, so that accumulation of energy continues in a positive nutritional environment (Hales & Barker, 2001). This has been supported by the results of several population-based studies. Studies on the Dutch Famine in 1944–1945 have shown that individuals exposed to inadequate nutrition during early gestation have a higher risk of developing obesity and coronary disease as adults when compared to those with adequate early nutrition (Painter, Roseboom, & Bleker, 2005). Other examples from different parts of the world, include the population exposed to the famine in Biafra during the Nigerian civil war (1967–1970) in which fetal and infant under-nutrition have been shown to be associated with increased risks of overweight, hypertension and type 2 diabetes in adulthood (Hult et al., 2010) and the Chinese Great Famine (1959–1960) with corresponding findings (Li et al., 2010; Liu et al., 2017; Wang, Wang, Lei, Xiao, & Luo, 2012).
2.2 Preterm birth

Preterm birth (before 37 full gestational weeks), which every year complicates around 14.9 million pregnancies (11% of all live births) (Blencowe et al., 2012), is the most frequent cause of perinatal problems and infant death worldwide (March of Dimes, mNCH, Save the Children, & WHO, 2012). With the growing number of preterm births (Blencowe et al. 2012) and advances in prenatal care, the numbers of adults born preterm have increased rapidly (Raju, Buist, Blaisdell, Moxey-Mims & Saigal, 2017). At the same time the adverse long-term consequences of preterm birth on health and wellbeing in older age have become visible.

Preterm birth may be a consequence of medical conditions of the mother or fetus, genetic influences, environmental exposure, behavioral and socioeconomic factors, infertility treatments or iatrogenic (medical treatment related) prematurity (Goldenberg, Culhane, Iams, & Romero, 2008). Preterm birth-related complications are the cause of death of more than one million children annually (Liu et al., 2012). Additionally, being born preterm predisposes an individual to a wide range of health risks along the course of life (Table 1) (Raju et al., 2017; Kumar 2017; Blencowe et al., 2012). In Finland fairly recently, 5.7% of newborns were born prematurely and 0.7% were born at a very low birth weight (VLBW, birth weight < 1500g) (THL, 2017). These numbers have remained relatively stable in recent years.

2.2.1 Classification of preterm birth

Preterm birth can be classified in separate categories according to completed pregnancy weeks. The World Health Organization (WHO) classifies it as: extremely preterm birth (<28 weeks), very preterm birth (28 to <32 weeks) and moderate to late preterm (32 to <37 weeks) (Blencowe et al., 2012). Late preterm birth more specifically refers to birth at 34 to <37 weeks (Loftin et al., 2010). In this work the term early preterm birth is used for births at <34 weeks (Sipola-Leppänen, 2015).

Categorization of preterm infants can also be based on birth weight: extremely low birth weight, ELBW (<1000 g), very low birth weight, VLBW (<1500 g) and low birth weight, LBW (<2500 g). The definition based on birth weight, however, does not take in account the gestational age at the time of birth. Low birth weight can be a consequence of preterm birth or a fetus can be already growth restricted before birth. The term “small for gestational age” (SGA) is therefore used usually
for infants who have a birth weight of more than -2 standard deviation (SD) below the mean birth weight for gestational age.

### 2.2.2 Long-term consequences of preterm birth

Longitudinal follow-up studies concerning the health of preterm-born subjects have shown that preterm birth predisposes an individual to a wide range of health risks in later life (Table 1). As most of the follow-up studies have mainly involved subjects born very preterm or with VLBW, most of the evidence of the long-term health effects of preterm birth is seen within this group. There is also, however, growing evidence of the long term effects of late preterm birth (Loftin et al., 2010). The morbidity related to preterm birth is often inversely related to gestational age so the most severe morbidities are seen in those born early preterm.

**Table 1. Long-term consequences of preterm birth**

<table>
<thead>
<tr>
<th>Aspects of health and wellbeing</th>
<th>Consequences</th>
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<tbody>
<tr>
<td>Cardiovascular health</td>
<td>Increased blood pressure</td>
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<td></td>
<td>Impaired vascular growth</td>
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<td>Metabolic health</td>
<td>Abnormal lipid profiles</td>
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<td>More abdominal tissue</td>
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<td></td>
<td>Abnormalities in insulin function</td>
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<tr>
<td>Asthma &amp; allergies</td>
<td>Higher risk of asthma and allergies</td>
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<td>Kidney health</td>
<td>Diminished renal function</td>
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<td>Mental health</td>
<td>Increased anxiety and depression</td>
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<td></td>
<td>Higher risk of hospitalisation for mental disorders</td>
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<td>Neurosensory and cognitive function</td>
<td>Declined motor development</td>
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<td>Increased risk of cerebral palsy, intellectual disability and neurosensory deficits</td>
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<td>Higher risk for reduced IQ</td>
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<tr>
<td>Social wellbeing</td>
<td>Difficulties in peer relationships</td>
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<td>Lower income levels</td>
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Modified from Raju et al., 2017 and Kumar 2017

**Metabolic consequences of preterm birth**

Metabolic syndrome is related to central obesity, dyslipidemia, hypertension, and insulin resistance. All of these factors increase the risk of type 2 diabetes and cardiovascular diseases. (Huang, 2009.) Adults born preterm have been shown to
have a higher risk of developing metabolic syndrome when compared with adults born at term. Preterm birth is associated with most of the factors associated with metabolic syndrome such as abnormal distribution of body fat (Breukhoven, Kerkhof, Willemsen, & Hokken-Koelega, 2012; Morrison et al., 2016; Sipola-Leppänen et al., 2015), abnormal lipid profiles (Parkinson, Hyde, Gale, Santakumaran, & Modi, 2013; Sipola-Leppänen et al., 2015), high blood pressure (Hovi et al., 2016; Parkinson et al., 2013) and abnormalities in insulin function (Hofman et al., 2004; Hovi et al., 2007; Kajantie et al., 2015).

A greater amount of abdominal adipose tissue, which seems to play an important role in the pathogenesis of the metabolic syndrome, has been seen in those born preterm when compared with term-born controls, and this has been observed as early as in infancy (Uthaya et al., 2005). Studies carried out to assess the body composition of adults have shown increased fat mass in those born preterm when compared with term-born controls (Breukhoven et al., 2012; Sipola-Leppänen et al., 2015; Thomas et al., 2011). This difference is also present in those born late preterm (Sipola-Leppänen et al., 2015). When fat distribution is examined more closely preterm-born adults have higher percentages of fat in the abdominal subcutaneous tissue, the liver and the pancreas (Crane et al., 2016).

The studies on lipid metabolism in adults born preterm are fewer. However a meta-analysis involving five studies with a total of 474 preterm-born participants revealed significantly higher levels of fasting LDL in those born preterm when compared with controls (Parkinson et al., 2013).

One consistent finding regarding adult-age outcomes of preterm birth is higher blood pressure when compared with adults born at term (de Jong, Monuteaux, van Elburg, Gillman, & Belfort, 2012; Hovi et al., 2016). A large multinational pooled sample provided estimates of 3.4 mmHg (95% CI 2.2, 4.6) higher systolic and 2.1 mmHg (95% CI 1.3, 3.0) higher diastolic blood pressure in those born preterm with VLBW when compared with adults with normal birth weight (Hovi et al., 2016). An association between preterm birth and insulin resistance in adulthood has also been shown in many populations (Hovi et al., 2007; Morrison et al., 2016; Rotteveel, van Weissenbruch, Twisk, & Delemarre-Van de Waal, H A, 2008).

Energy imbalance is an important factor in the development of obesity. A positive energy balance leads to accumulation of fat and weight gain, further leading to overweight, obesity and other metabolic disorders (Hill, 2006). It has been found that adults born preterm with VLBW have lower resting energy expenditure (REE) but higher REE per unit of lean body mass when compared with adults born at term (Sipola-Leppänen et al., 2011). It has been proposed that this
higher metabolic rate could on the other hand protect those born preterm from development of metabolic syndrome.

Lifestyle, including physical activity and diet, is the most important factor contributing to energy balance and further to the development of obesity and metabolic syndrome. One of the proposed mechanisms acting behind the association of preterm birth and later metabolic disorders is the unfavourable lifestyle choices of those born preterm. Previous literature has suggested that those born preterm have lower muscular fitness and report lower levels of physical activity (Kajantie et al., 2010; Tikanmäki, Kaseva et al., 2017) although this difference has not been verified by objective measurement (Kaseva et al., 2015; Tikanmaki, Tammelin et al., 2017). Young adults born preterm or at VLBW have also been shown to have unfavourable dietary preferences which may in part contribute to their increased risk of metabolic disorders (Kaseva et al., 2013; Sharafi et al., 2016). However, studies are few and the results are conflicting. In a recent review it was concluded that current evidence does not support an association of early-life growth with energy balance-related behaviour patterns in later life (van Deutekom, Chinapaw, Jansma, Vrijkotte & Gemke, 2017). Thus, more high-quality studies related to these risk factors, and whether they are also present in those born late preterm are needed in order to develop effective intervention strategies possibly preventing future cardiometabolic diseases in the preterm population.

2.2.3 Early nutrition after preterm birth

Nutrition is a key factor in ensuring healthy growth, metabolism and immunity in a preterm infant because such an infant is born during the time when growth is maximal and the requirements for energy and nutrients are the highest. Furthermore, physiological immaturity of a preterm-born infant poses a challenge as regards early nutrition. Sufficient nutrition is often provided by combining enteral and parenteral nutrition.

Breastfeeding is associated with many positive health outcomes (Victora et al., Lancet 2016) and maternal milk fortified with additional minerals and protein is the recommended form of nutrition for preterm-born infants (Agostoni et al., 2010; Kumar et al., 2017). In such infants, however, sufficient maternal milk is not always available; thus they are often also fed donor breast milk or artificial formula. Using donor breast milk instead of formula has many health benefits and it has been associated with a shorter time to full enteral feedings (Kreissl et al., 2017) and
higher breastfeeding rates at discharge (Wilson, Christensson, Brandt, Altman, & Bonamy, 2015). However, donor breast milk varies in the content of energy, protein and fat, depending on the stage of lactation when it is expressed (Saarela, Kokkonen, & Koivisto, 2005), some nutritional elements may be inactivated by the pasteurization process (Hanson, Lyden, Furtado, Van Ormer, & Anderson-Berry, 2016) and the diet of the lactating mother influences the composition of expressed milk (Innis, 2014). Consequently, nutrient fortification of breast milk is now a common practice in neonatal care. An adequate protein to energy ratio is essential in the nutrition of a preterm infant. When too little is provided, sufficient postnatal growth is compromised, which may result in postnatal growth failure and altered body composition (Cooke & Griffin, 2009; Roggero et al., 2009) as well as poorer neurocognitive functioning (Sammallahti et al. 2014) of preterm infants. However, over-nourishing and consequently promoting postnatal weight gain has also been shown to be detrimental (Kerkhof, Willemsen, Leunissen, Breukhoven, & Hokken-Koelega, 2012).

Although the nutrition of preterm-born infants has been studied widely during the last two decades with regularly updated guidelines (Agostoni et al., 2010), the reports still show inadequate nutritional intake and growth restriction in these infants (Corpeleijn, Vermeulen, van den Akker, Chris H, & van Goudoever, 2011; Lapillonne, Carnielli, Embleton, & Mihatsch, 2013). In particular, the protein requirements of infants born preterm have been a challenging problem for neonatologists since the early advances in neonatal care. Human milk was recommended for preterm infants until the 1940’s. As the nutritional recommendations for preterm-born infants have been aimed for continuing growth at the intrauterine rate, formulas with protein supplementations were introduced when better weight gain with formulas was found. However, later studies revealed that increased protein content can also have metabolic disadvantages and human milk with protein supplementation has been the recommended form of feeding ever since. (American Academy of Pediatrics, 1985; American Academy of Pediatrics, Committee on Nutrition, 1976; American Academy of Pediatrics, Committee on Nutrition, 1977.)

Studies on the long-term effects of early nutrition have shown that one major challenge in feeding preterm infants is the trade-off between better cognitive outcomes and increased risks of metabolic and cardiovascular diseases (Belfort, Gillman, Buka, Casey, & McCormick, 2013). Although much progress has been made, there is still a lack of sufficient data to allow decision on the optimal macronutrient intakes for preterm infants (Harding et al., 2017).
2.3 Nutritional programming

Under the DOHaD-theory, adverse fetal and early infant nutrition can lead to subsequent development of risks of metabolic health in later life (Langley-Evans, 2015; Reynolds, Gray, Li, Segovia, & Vickers, 2015). On the other hand, preterm birth has been suggested to play a role in building adult body image, eating habits and food preferences.

2.3.1 Programming of adult body composition and energy metabolism by early nutrition

In animal studies, it has been consistently shown that neonatal nutrition and growth patterns play an important role in programming adult metabolic state. Human evidence is limited but exists. Both animal and human studies have shown that metabolic programming of energy balance begins with and can be modified by nutrition in the early stages of life. This observation has led to increasing interest in pregnancy and lactation as critical periods of development. As early as in the 1990’s Plagemann and colleagues showed in animal studies that neonatal over-nutrition results in an adult phenotype with increased food intake, an increased risk of becoming overweight, increased fat deposition, hyperinsulinaemia and impaired glucose tolerance (Plagemann, Heidrich, Gotz, Rohde, & Dorner, 1992; Plagemann et al., 1999). These studies were followed by many others with similar results, as reviewed by Habbout, Li, Rochette and Vergely (2013). In assessing the long-term effects of early nutrition, most human studies have relied on proxies, owing to ethical restrictions and the fact that direct data on early nutrition has not been available. The few exceptions include trials carried out to assess the long-term effects of protein content in infant formula (Singhal et al., 2010), and observational studies in those born preterm at VLBW whose nutrient intake during their neonatal hospital stay is recorded in detail (Ludwig-Auser et al., 2013; Regan, Cutfield, Jefferies, Robinson, & Hofman, 2006).

The largest body of evidence relating early nutrient intake to later health in humans has been obtained by using birth weight and early-growth trajectories as proxies for fetal and neonatal nutrient intake (Koletzko, Symonds, Olsen, Early Nutrition Programming Project, & Early Nutrition Academy, 2011; Wells, Chomtho, & Fewtrell, 2007). Also, historical episodes of hunger such as the Dutch Famine, the Biafran Famine and the Chinese Great Famine have served as natural experiments on the effects of nutritional deprivation during pregnancy on the future
risk of diabetes and other cardiometabolic diseases in the offspring (de Rooij, Roseboom, & Painter, 2014). Next, the evidence linking early nutrition, partly via proxies such as birth weight and early growth, to adult metabolic health is reviewed.

**Body composition**

The human body is composed of lean body mass including muscle, bone and extracellular water and metabolically less active adipose tissue primarily composed of storage fat (Willett & Hu, 2013). In epidemiological research, overweight conditions and obesity are often examined by using the most commonly available anthropometric measures, weight, body mass index (BMI, weight/height²) and waist circumference. As body weight varies considerably depending on the amount of lean and fat mass, body weight and BMI are not ideal measures for assessing body composition (Müller et al., 2012). Of the more precise methods, body composition is measured in research settings mainly by 1) Dual-Energy X-ray Absorptiometry (DXA) which distinguishes fat mass, fat-free mass and bone-mineral mass by the different absorption of the high- and low-energy X-rays by these tissues (Shepherd, Ng, Sommer, & Heymsfield, 2017), or 2) Bioelectrical Impedance Analysis (BIA) which is based on the principle that electricity is conducted differently in fat and lean tissues (Böhm & Heitmann, 2013). Both of these techniques have been widely shown to be valid tools for estimating body composition in healthy adults (Bosy-Westphal et al., 2013; Seabolt, Welch, & Silver, 2015).

In studies carried out to assess the role of early nutrition in adult outcomes, maternal obesity and gestational diabetes have been used as markers of fetal nutrition. It has been consistently shown that offspring exposed to maternal gestational diabetes are more likely to develop obesity or insulin resistance in later life when compared with offspring of metabolically healthy mothers (Damm et al., 2016). There is also clear evidence suggesting that maternal pre-pregnancy obesity as well as excessive gestational weight gain are associated with an increased risk of obesity in offspring (Godfrey et al., 2017).

The association between birth weight and BMI in adulthood has been assessed in two systematic reviews. Both of them revealed a positive association between birthweight and obesity in later life (Parsons, Power, Logan, & Summerbell, 1999; Rogers & EURO-BLCS Study Group, 2003). However, as BMI does not take into account the ratio of lean and fat mass, it is not considered to be a very reliable measure of body composition. These systematic reviews were therefore followed
by studies carried out to assess body composition by using more precise measures, such as DXA (Bann et al., 2014), skin-fold thickness (Sayer et al., 2004) and BIA (Ylihärsilä et al., 2007). These studies revealed that low birth weight is associated with lower lean body mass (LBM) (Bann et al., 2014; Sayer et al., 2004; Ylihärsilä et al., 2007) and when adjusted for adult BMI, also with higher body fat percentage (Ylihärsilä et al., 2007).

Three systematic reviews assessing the association between early growth and body composition concluded that individuals who grew rapidly during infancy were at increased risk of subsequent obesity as early as in childhood and also in adulthood (Baird et al., 2005; Monteiro & Victora, 2005; K. K. Ong & Loos, 2006). The link between rapid weight gain in infancy (Deemerath et al., 2009; Dubois & Girard, 2006; Karaolis-Danckert et al., 2006; Kerkhof, Leunissen, & Hokken-Koelega, 2012; Leunissen, Kerkhof, Stijnen, & Hokken-Koelega, 2009; Oyama, Saito, & Nakamura, 2010; Salgin et al., 2015) and childhood (Fall et al., 2008; Sutharsan, O’Callaghan, Williams, Najman, & Mamun, 2015; Ylihärsilä et al., 2008) and the increased risk of an overweight condition and obesity in later life has also been confirmed in a number of more recent studies.

Regarding the direct evidence linking early nutrition to adult body composition, the most extensive evidence comes from studies assessing the association between breastfeeding and adult health. Convincing evidence has been presented in multiple systematic reviews and meta-analyses of a small association between breastfeeding and a reduced risk of obesity in childhood. In a meta-analysis published in 2007, breastfed individuals were less likely to be considered as overweight and/or obese (OR 0.78, 95% CI 0.72–0.84), independent of confounding factors. This association was not, however, seen in adult age (Horta et al., 2007). A recent update on that meta-analysis with 60 additional studies observed an association between breastfeeding and lower prevalence of overweight/obesity later in life (OR 0.88 [0.83–0.93]) (Horta & Victora 2013). Other studies reaching to young adulthood and beyond have not confirmed this association or have yielded mixed results (De Kroon et al., 2011; Kvavik, Tell, & Klepp, 2005; Parsons, Power, & Manor, 2003; Victora, Barros, Lima, Horta, & Wells, 2003; Zamora-Kapoor et al., 2017). The systematic review by Horta and Victora (2013) suggested that the effect might be gradually diluting with time (OR in 1 to 9 year old individuals 0.77 [0.83–0.93], in 10 to 19 year old individuals 0.62 [0.53–0.73] and in individuals over 20 years 0.89 [0.84–0.96]).

The early protein hypothesis links early nutrition directly to adult metabolic outcomes and suggests that high protein intakes in the first months of life increase
the risk of subsequent obesity (Koletzko et al., 2005). The EU Childhood Obesity Project (CHOP) investigates the association between protein/fat ratio in infant formula and obesity risk in later life. The original trial was a one-year multicentre intervention trial concerning infants born at term in five countries with different habitual total protein intakes (Koletzko et al., 2009; Weber et al., 2014). In the most recent follow-up at six years of age, the risk of becoming obese was 2.43 (95% CI: 1.12, 5.27; p = 0.024) times higher in the group exposed to higher protein intake (2.05 compared with 1.25 g/dL in infant formula and 3.2 compared with 1.6 g/dL in the follow-up formula) in infancy (Weber et al., 2014).

Objective recordings of early nutrition have been used in a study examining the influence of early energy and protein provision in preterm infants (n=51) on adolescent body composition, in which participants were divided into groups depending on infant energy and protein provision during the first 14 days of life. In that study those who received more energy in early life were significantly taller and heavier in adolescence. Early protein intake was not associated with adolescent body size. (Ludwig-Auser et al., 2013) The number of participants was however rather low in that study.

Although a consistent association between early nutrition and growth and adult metabolic health has been found, it still remains to be elucidated how these act together. Recent studies have focused on the growth trajectories rather than single measures in weight gain in early life. A few recent studies have also assessed the associations between early growth, nutrition and later body size (Johnson, van Jaarsveld, Llewellyn, Cole, & Wardle, 2014; Rzehak et al., 2017). A study carried out to examine growth velocity and tempo during the first year of life in association with breastfeeding and early weaning revealed that those breastfed for longer grew more slowly and for longer after birth, but still reached the same body size as infants who were never breastfed (Johnson et al., 2014). As previously reviewed, this slower growth may be beneficial as regards the risk of obesity and related disorders in later life. Studies on early nutrition and growth with longer follow-up periods and the ability to control for more confounding factors are needed as there is lack of studies in which diet is examined very closely or in connection with growth, and where individuals are followed into adulthood.

Resting energy expenditure

Energy is needed for basal metabolic functions, such as breathing, blood circulation and neural functioning. Factors affecting resting energy expenditure (REE) are age,
sex, the amount of lean body mass, thermogenesis and the amount and intensity of physical activity (Willett, 2013b). REE can be measured by Indirect Calorimetry, in which energy expenditure is calculated from oxygen uptake and carbon dioxide production, using established equations. Another measurement method is the Doubly Labelled Water (DLW) method, which is very precise and is considered to be the gold standard in measurements of REE. Indirect calorimetry, however, is also very precise and more convenient in use in epidemiological research settings when compared with the DLW method (Pinheiro Volp, Esteves de Oliveira, F C, Duarte Moreira Alves, Esteves, & Bressan, 2011).

There is evidence from animal studies that environmental effects early in life may affect resting energy expenditure in adulthood (Criscuolo, Monaghan, Nasir, & Metcalfe, 2008; Verhulst, Holveck, & Riebel, 2006). In mice, early postnatal overfeeding leads to reduced resting energy expenditure (Li et al., 2013). In humans, the studies are confined to the association between birth weight and later REE and have mainly been published by our study group. Lower birth weight has been linked to higher REE (Eriksson, Forsen, Tuomilehto, Osmond, & Barker, 2002), with sex-specific differences (Sandboge et al., 2012). Young adults born preterm at VLBW, on the other hand, have lower REE but a higher REE/LBM ratio when compared with term-born counterparts (Sipola-Leppänen et al., 2011), suggesting that they might have more metabolically active tissue than peers born at term. It has been shown that the metabolically most active organs, such as the brain (Lemola et al., 2017), are smaller in VLBW adults.

### 2.3.2 Programming of food intake and appetite

There is considerable evidence from experimental animal studies that food preferences are already partly programmed during fetal and early postnatal life (Dalle Molle, Bischoff, Portella, & Silveira, 2015; Gugusheff et al., 2015; Portella et al., 2012). Studies have shown that rats growth-restricted during fetal life and nursed in small litters showed catch-up growth and an increased preference for energy-rich and palatable foods i.e. foods with a more pleasant or agreeable taste (Bayol, Farrington, & Stickland, 2007). In humans, the evidence is more scarce and heterogeneous (Table 2). However, it has been shown that young women who have suffered from severe intrauterine growth restriction (IUGR), have a higher intake of carbohydrates, and a preference for carbohydrate over protein as adults when compared with peers born after normal pregnancies (Barbieri et al., 2009). Adults who have suffered from maternal famine during pregnancy, have a higher energy
intake and a higher fat density in the diet (Stein, Rundle, Wada, Goldbohm, & Lumey, 2009) and have also been shown to be more prone to consume a high-fat diet at an older age (Lussana et al., 2008). These results are in line with those of animal studies suggesting that early-life adversities increase the preference for energy-rich and palatable foods.

Studies have shown that young adults born preterm at VLBW consume markedly fewer fruits and berries as well as milk products than term-born peers (Kaseva et al., 2013). A similar study on the association between birth weight and food and nutrient intake at an older age in term born individuals revealed that lower birth weight was associated with lower intake of fruits and vegetables (Perälä et al., 2012). Furthermore, in a recent study carried out to compare dietary behaviours and preferences in preterm versus term-born adults by using a healthy eating preference index, adults born preterm reported a lower dietary quality, driven by a lower preference for protein-rich foods and a tendency towards a greater liking for sweets (Sharafi et al., 2016).

When reviewing the literature on studies on food intake and food preferences, the measurement method needs to be taken in account. In research settings the most commonly used methods are food records and food frequency questionnaires (FFQs). Food records are based on precise reporting of all foods and amounts actually consumed by an individual over a predefined time period (often one to three days). A FFQ on the other hand consists of a food list and a frequency reporting section and is based on measuring the average long-term diet. Food records are more specific in describing foods, but they are rather time-consuming to conduct. Thus, in epidemiological studies use of FFQs, as self-administered and easy-to-process forms, has become the primary method for measuring dietary intake (Baranowski, 2013; J. Shim, Oh, & Kim, 2014; Willett, 2013a). The overall patterns of the diet can also be examined by a priori indices. These are usually based on published healthy-eating guidelines and concern the intake of main foods or food groups reflecting dietary reference values (Cespedes & Hu, 2015; Hu, 2002).
### Table 2. Studies on the early origins of food intake

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>No. of subjects; age</th>
<th>Exposure</th>
<th>Main methods</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barbieri et al., 2009</td>
<td>2063, 24 y</td>
<td>IUGR FFQ</td>
<td>Higher intake of carbohydrate in young women born with severe IUGR. Preference for carbohydrate over protein in IUGR group.</td>
<td></td>
</tr>
<tr>
<td>Stein et al., 2009</td>
<td>655, 58 y</td>
<td>Famine FFQ</td>
<td>Positive association between famine exposure and higher energy intake and higher fat density in diet at adult age.</td>
<td></td>
</tr>
<tr>
<td>Lussana et al., 2008</td>
<td>730, 58 y</td>
<td>Famine FFQ</td>
<td>Those exposed to famine were twice as likely to consume high-fat diet.</td>
<td></td>
</tr>
<tr>
<td>Perälä et al., 2012</td>
<td>56-70 y</td>
<td>Birth size (birth weight, ponderal index) FFQ</td>
<td>Small size at birth was associated with lower consumption of fruits, berries, rye and rye products as well as increased proportion of daily energy intake from fat and lower intake of carbohydrates (sucrose, fructose and fibre).</td>
<td></td>
</tr>
<tr>
<td>Kaseva et al., 2013</td>
<td>151 VLBW / 161 controls, 19-27 y</td>
<td>VLBW 3-day food record</td>
<td>Reduced consumption of vegetables, fruits and berries, milk products and low-fat dairy products in VLBW participants.</td>
<td></td>
</tr>
<tr>
<td>Matta et al., 2016</td>
<td>229 AGA/172 SGA, ~22 y</td>
<td>SGA/AGA A food questionnaire with 19 items</td>
<td>SGA-born adults consumed more meat and sugar and less fish than AGA-born individuals. No differences between the groups in adherence to recommended guidelines.</td>
<td></td>
</tr>
<tr>
<td>Sharafi et al., 2016</td>
<td>129 Preterm birth</td>
<td>Preterm food list and healthy eating preference index</td>
<td>Dietary quality mediated the association between term status and HDL-cholesterol.</td>
<td></td>
</tr>
<tr>
<td>Doornweerd et al., 2017</td>
<td>78 + 94 twin pairs, 13-22 y</td>
<td>Birth weight Two-day dietary records</td>
<td>Lower birth weight was associated with higher intake of energy and saturated fat.</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AGA, appropriate for gestational age; FFQ, Food frequency questionnaire; IUGR, intrauterine growth restriction; VLBW, very low birth weight; SGA, small for gestational age
2.3.3 Developmental origins of eating disorders

Eating Disorders (EDs), including anorexia nervosa (AN) and bulimia nervosa (BN), are among various psychiatric conditions which have been suggested to originate partly from adverse birth outcomes and early life. The prevalence of eating disorders in Finland is 2.2% for AN (Keski-Rahkonen et al., 2007) and 2.3% for BN (Keski-Rahkonen et al., 2009). Anorexia nervosa is characterized by fear of weight gain and a distorted view of one’s body size and shape. Bulimia nervosa includes recurrent binge-eating episodes and regular self-induced vomiting or laxative or diuretic misuse. A distorted body image also characterizes patients suffering from BN. Extremely low weight is characteristic of AN, but patients with BN often have normal BMI or even a tendency to be overweight. Individuals with AN eat substantially fewer calories when compared with normal-weight controls, whereas individuals with BN consume more calories when compared with normal-weight or even obese controls. However, dysfunctional eating patterns characterize both of these disorders (Forbush & Hunt, 2014).

The aetiology of eating disorders is multifactorial, including multiple genetic and environmental factors (Fairburn & Harrison, 2003). Studies on the early developmental origins of eating disorders have yielded somewhat inconsistent results, although, pregnancy and neonatal characteristics have been repeatedly suggested to play a role (Table 3) (Cnattingius, Hultman, Dahl, & Sparen, 1999; Favaro, Tenconi, & Santonastaso, 2006). Preterm birth, partly in a dose-response manner (Goodman, Heshmati, Malki, & Koupil, 2014), has been associated with anorexia nervosa (Cnattingius et al., 1999; Foley, Thacker, Aggen, Neale, & Kendler, 2001; Lindberg & Hjern, 2003) or related symptomatology (Micali et al., 2015). However, a recent meta-analysis summarising six studies on the association between obstetric complications and prematurity, and EDs, revealed no connection between preterm birth and AN (OR 1.17, 95% CI 0.91–1.52) (Krug, Taborelli, Sallis, Treasure, & Micali, 2013). In addition, in a descriptive review assessing the literature on prenatal and perinatal factors associated with EDs it was concluded that evidence regarding an association between preterm birth and AN exists, but is somewhat contradictory (Raevuori, Linna, & Keski-Rahkonen, 2014). However, the results of a study by our group suggested that young adults born preterm at VLBW have a healthier body image and fewer traits related with eating disorders when compared to term-born peers (Wehkalampi et al., 2010).

The difficulty in reviewing the literature on the risk of eating disorders in preterm-born adults is that the risk of EDs has been defined in various ways. In
research settings, in addition to actual ED diagnoses, mainly three different questionnaires have been used, namely the; Eating Disorder Inventory-2 (EDI-2), the Eating Attitudes Test (EAT) and the Eating Disorder Examination-Questionnaire (EDE-Q). Questionnaires are economical and time effective to use and although not always as accurate as face-to-face interviews, their validity is well documented (Spillane, Boerner, Anderson, & Smith, 2004; Türy, Güleç, & Kohls, 2010).

Table 3. Studies on the association between preterm birth and later eating disorders

<table>
<thead>
<tr>
<th>Authors, year</th>
<th>Eating disorder, diagnosed/symptoms</th>
<th>Study population</th>
<th>Exposures</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cnattingius et al., 1999</td>
<td>ED diagnosed / AN</td>
<td>781 AN / 3905 controls</td>
<td>Gestational age, birth weight</td>
<td>Increased risk of AN in girls born VPT</td>
</tr>
<tr>
<td>Favaro et al., 2006</td>
<td>ED diagnosed / AN + BN</td>
<td>114 AN/73 BN/554 controls</td>
<td>Gestational age, birth weight</td>
<td>SGA was significantly associated with BN</td>
</tr>
<tr>
<td>Feingold et al., 2002</td>
<td>Eating disorder symptoms: EDI-2, EAT</td>
<td>53 preterm born adults</td>
<td>Preterm birth</td>
<td>No associations</td>
</tr>
<tr>
<td>Foley et al., 2011</td>
<td>ED diagnose / AN+BN</td>
<td>78 AN / 142 BN / 1524 other psychiatric diagnoses</td>
<td>Gestational age, birth weight</td>
<td>GA associated with an increased risk of AN</td>
</tr>
<tr>
<td>Goodman et al., 2014</td>
<td>ED diagnosed / AN/ BN</td>
<td>Population cohort, register data 2,015,862</td>
<td>Gestational age,</td>
<td>A clear dose-response relationship between GA and AN</td>
</tr>
<tr>
<td>Lindberg et al., 2003</td>
<td>ED diagnosed / AN</td>
<td>Population cohort n=989,871</td>
<td>Gestational age, birth weight</td>
<td>Increased risk of AN in individuals born preterm</td>
</tr>
<tr>
<td>Micali et al., 2015</td>
<td>EDE-Q</td>
<td>143 VPT individuals</td>
<td>Gestational age, birth weight</td>
<td>Higher ED psychopathology in VPT individuals</td>
</tr>
<tr>
<td>Nicholls and Viner, 2009</td>
<td>Self-reported AN</td>
<td>101 AN / 10906 controls</td>
<td>Prematurity, birth weight</td>
<td>No associations</td>
</tr>
<tr>
<td>Wehkalampi et al., 2011</td>
<td>Eating disorder symptoms: EDI-2</td>
<td>163 VLBW / 189 controls</td>
<td>Birth weight</td>
<td>VLBW participants scored lower in EDI indicating fewer traits related to ED</td>
</tr>
</tbody>
</table>

Abbreviations: AN Anorexia Nervosa; BN Bulimia Nervosa, GA Gestational Age; ED Eating Disorder; EAT Eating Attitudes Test; EDI-2 Eating Disorder Inventory-2; EDE-Q Eating Disorder Examination-Questionnaire; VLBW Very Low Birth Weight; VPT Very Preterm.
2.3.4 Mechanisms behind nutritional programming

The specific underlying pathogenic mechanisms behind early nutritional programming, or programming of food intake and appetite are mainly unknown. However, animal studies have given some mechanistic insight and have suggested that programming effects are driven mainly by permanent structural changes in key metabolic organs, long-term changes in hormonal function and epigenetic regulation (Langley-Evans, 2015) (Figure 1).

Key metabolic tissues include the brain, adipose tissue and pancreas. Early nutrition plays an important role in tissue remodelling. Human examples of the programming of organ structures are, for example, a lower number of nephrons in those exposed to an altered early environment affecting their risk of later cardiovascular disease (Gurusinghe, Tambay, & Sethna, 2017) or altered fat deposition in those exposed to maternal obesity in utero, exposing them to later metabolic disorders (Leonard, Rasmussen, King & Abrams, 2017).

The hypothalamus plays an important role in energy balance regulation (Williams, Harrold, & Cutler, 2000). Leptin metabolism and changes in hypothalamic development are among the main mechanisms suggested to be responsible for the early programming of food intake and appetite. Appetite is regulated predominantly in the brain at the arcuate nucleus with a few hypothalamic neuropeptides responsible for controlling food intake. The adipokine leptin and its regulation have been shown to be critical for the normal development of tissues and related signaling pathways. Leptin acts at different levels of the central nervous system and has an important role in regulating energy intake, balancing appetite and promoting energy expenditure (Fulton et al., 2006; Jéquier, 2002). Interestingly, leptin resistance has been found in preterm-born individuals in infancy (Duncan, Frankfurt, Heyne, & Rosenfeld, 2017). It has also now been shown in a number of animal studies that leptin deficiency during critical windows of development has long-term effects in the control of appetite (Vickers & Sloboda, 2012). Moreover, altered early nutrition increases the production and sensitivity to the appetite peptide, neuropeptide Y and decreases those of the satiety peptide proopiomelanocortin (Diane et al., 2014).
Fig. 1. Possible mechanisms behind the programming of the metabolic syndrome (adapted from Fall, 2011). Abbreviations IGF-1, insulin-like growth factor-1, HPA axis, Hypothalamic–pituitary–adrenal axis

Experimental animal studies have also indicated that altered fetal and early-life nutrient intake may cause disruptions in the development of the central mesolimbic reward system (Ong & Muhlhausler, 2011). This includes the opioid and dopamine pathways, which have been shown to affect food preferences and eating habits in later life with a preference for energy-dense foods and excess food intake, resulting in weight gain and related disorders. Leptin also modulates the activity of mesocorticolimbic dopamine neurons which have also been shown to be modified by early life nutrition (Alves, Dalle Molle, Desai, Ross, & Silveira, 2015; Dalle Molle et al., 2015).

Metabolic imprinting, occurring via induced alterations in epigenetic gene regulation, is one of the most cited potential mechanisms behind the programming of regulation of energy balance. Various mechanisms, including DNA methylation, participate in epigenetic regulation. Evidence exists showing that exposures during early development induce alterations in DNA methylation persisting to adulthood (Domínguez-Salas et al., 2014; Waterland, 2014). Early-life exposures influence
the epigenome by controlling for gene expression through silencing modified alleles without changing the DNA sequence itself. It is suggested that this might contribute to a process in which exposures during early life are fixed in later life, long after the exposure itself, leading to changes in gene expression affecting the function of the human body, including the regulation of energy balance. (Guilloteau, Zabielski, Hammon, & Metges, 2009; Langley-Evans, 2015.)

In human studies providing mechanistic clues on the programming of food preferences, the results are still few, but for example it has been shown that fetal growth restriction alters the hedonic response as early as at birth (Ayres et al., 2012) and may thus lead to altered food preferences later in life. Understanding these factors might provide opportunities in early prevention of the cardiometabolic risks related to preterm birth.

2.4 Summary and hypotheses

The literature reviewed above suggests that adults born preterm have a higher risk of metabolic syndrome when compared with term-born peers, and infant feeding has a role to play in programming of adult metabolic health and diet. Most of the evidence linking early nutrition to later metabolic health comes from animal studies or human studies relying on proxies, such as birthweight or early growth. There is a limited amount of long-term data on human studies with objective recordings of early nutrient intake. In addition, past studies show that eating habits and food preferences may already be partly programmed during infancy and early childhood. The results, however, are somewhat inconsistent and are confined to those born at the lowest range of gestational ages.

The overarching hypothesis in this doctoral thesis is that food and nutrient intake and body image, from early infancy to adulthood, have key roles in mediating and modifying the associations between preterm birth and adverse metabolic health in adult life.
3 Aims

The specific aims of this thesis, each assessed in separate publications (I–IV), were to examine:

1. the association between energy and macronutrient intake during hospital treatment after preterm birth and body composition, energy metabolism and food and nutrient intake in young adults born at VLBW (I and II)
2. traits related to eating disorders in young adults born preterm (III)
3. food and nutrient intake in young adults born preterm (IV)
4 Methods

This work is based on data from three different cohort studies: 1) The Helsinki Study of Very Low Birth Weight Adults (I, II) and 2) the ESTER Preterm birth study in combination with 3) the Arvo Ylppö Longitudinal Study (III, IV).

4.1 The Helsinki Study of Very Low Birth Weight Adults (I, II)

4.1.1 The study population

The Helsinki Study of Very Low Birth Weight Adults (HeSVA) (Hovi et al., 2007) is a prospectively collected longitudinal birth cohort study aimed at assessing how being born preterm at VLBW affects adult health and well-being. The original study cohort consisted of 335 consecutive infants born at VLBW (<1500 g) and cared for and discharged alive from the neonatal intensive care unit (NICU) of the Children’s Hospital at Helsinki University Central Hospital between January 1978 and December 1985. When the study cohort reached young adulthood (2004–2005), a comparison group was selected from hospital records of infants born at term and not SGA. Participants were group-matched for age, birth hospital and sex and were invited to take part in a clinical examination in Helsinki, to which 166 (65.1%) of the VLBW participants and 172 (54.8%) of the participants born at term agreed to participate. In the current work only the data for the VLBW participants from this cohort is used. A flowchart of the study participants is presented in Figure 2.

4.1.2 Neonatal data

Perinatal and neonatal data on the study participants were collected from the hospital records. We also collected detailed information on enteral and parenteral nutrition, medication, and blood transfusions the infant received and daily/weekly growth measurements from the records of the NICU or follow-up units. The daily nutritional intake during the initial hospital stay was collected from hospital records for 158 participants born preterm and who underwent the clinical examination (data was unavailable for eight participants). Complete hospital records were missing for 17 subjects and they were therefore excluded from the analyses. After the age of nine weeks there was a reduction in the number of participants with sufficient data because of discharges from the hospital. Hence, we
Fig. 2. Flowchart of the study participants of the Helsinki Study of Very Low Birth Weight Adults (Studies I and II). Abbreviations: NICU, Neonatal Intensive Care Unit, CP, Cerebral Palsy.
decided to limit the data to the first nine weeks of life. The 9-week data was then further divided into three 3-week periods. Participants with neurosensory impairments (n=14) were excluded from the main analyses because these conditions may impact body composition and metabolism. Weight measurements for the early weeks of life were collected from the hospital records. Daily measurements were interpolated from measurements around the seven consecutive days. The absolute values were transformed into SD units according to Finnish growth standards.

All study participants received pooled, banked, and pasteurized human milk during their initial stay at the NICU. Enteral feedings were begun through a nasogastric tube during the first or second day of life. The daily milk intake was thereafter increased according to individual tolerance until the amount of 200 ml/kg/d, which was then maintained until discharge. Calcium, phosphate, and multivitamin supplementations were used throughout the study period. Milk fortifiers or preterm formulas were also being introduced. Intravenous fluids (glucose, amino acids and lipids) were started when enteral feeding was not possible. We excluded medications and blood transfusions from the analysis.

To calculate the daily nutrient intakes, we used previously published figures for the macronutrient content of the mothers’ own breast milk (Anderson et al., 1983) together with measures drawn from preterm milk. The corresponding content for banked human breast milk was based on values published by Rönnholm and colleagues with macronutrient content analysed from pasteurized milk from the milk bank of the same hospital where the infants of the present study were treated (Rönnholm, Sipilä, & Siimes, 1982; Rönnholm, Simell, & Siimes, 1984). The contents of fortifiers were based on concentrations received from the manufacturers (Nutricia Baby Oy). For the contents of special preterm formulas or protein fortifiers we used data published during the matching time period in European countries (Brooke, Wood, & Barley, 1982; Modanlou, Lim, Hansen, & Sickles, 1986).

4.1.3 Questionnaires

The adult participants completed a detailed questionnaire covering medical history, use of medication, daily smoking habits, leisure-time physical activity and parental education.

The total energy intake at adult age was evaluated using a 3-day food record, which 155 VLBW participants completed (Kaseva et al., 2013; J. S. Shim, Oh, &
Kim, 2014). A trained study nurse instructed the participants to report everything they ate and drank at the times when food was eaten, over a 3-day period. A picture booklet was used to assist estimation of portion sizes (Haapa, Toponen, Pietinen, & Räsänen, 1985). After completing the food record, the participants were interviewed face-to-face by a nutritionist to ensure the completeness of the food records filled. Mean daily consumption of food items and intakes of energy, macronutrients and micronutrients were calculated by using a dietary analysis program based on the national food composition database, FINELI (Reinivuo, Hirvonen, Ovaskainen, Korhonen, & Valsta, 2010). We reported the total energy intake in units of kilocalories per day (kcal/d).

Leisure-time physical activity was assessed in terms of metabolic equivalent hours (MET) per week on the basis of a questionnaire concerning 1) light (assuming a value of 3 MET), 2) moderate to vigorous (5 MET), and 3) commuting physical activity (4 MET) (Kajantie et al., 2010).

4.1.4 Clinical examination

The participants attended a clinical examination at a mean age of 22.4 years. The examination included measurements of height and weight, according to which BMI was calculated. Waist circumference was measured midway between the lowest rib and the iliac crest. (Hovi et al., 2007)

Whole-body dual-energy X-ray absorptiometry (DXA) (software version 12.3:3, Hologic, Bedford, MA, USA) was used to measure body composition (n = 118) (Hovi et al., 2009). DXA measurement is based on distinguishing fat mass, fat-free mass and bone mineral mass by the differential absorption of high and low energy X-rays in different tissues. Resting energy expenditure (REE) was measured after an overnight fast at rest by indirect calorimetry (Deltatrac II; Datex, Helsinki, Finland) when the device was available (n = 96) (Sipola-Leppänen et al., 2011). Indirect calorimetry gives a measure of energy expenditure from measurements of oxygen uptake and carbon dioxide production.
4.2 The ESTER preterm birth study and the Arvo Ylppö Longitudinal Study (III, IV)

4.2.1 Study populations

The ESTER Preterm Birth Study

The ESTER study (Sipola-Leppänen, 2015) is a birth-cohort study of individuals born in the two northernmost provinces of Finland between 1985 and 1989. The cohort study was established in order to study the effects of preterm birth and maternal pregnancy disorders on the children’s health and wellbeing in adulthood. In the present work, only the participants in the ESTER Preterm Birth Study (Sipola-Leppänen et al., 2015) are included. Exposed participants, i.e. young adults born preterm (at < 37 weeks of gestation) were traced through the Northern Finland Birth Cohort (NFBC) 1986 or the Finnish Medical Birth Register (FMBR). Controls were randomly selected from the source populations. Of the 1980 invited participants, 779 took part in a clinical examination in 2009–2011 at a mean of 22.3 ± 1.3 (SD) years of age. They were further categorized into three groups according to their gestational age at birth; early preterm (<34 weeks of GA), late preterm (34 to <37 weeks of GA) and term-born controls. In the current work I will use data from 148 participants born early preterm, 246 participants born late preterm and 354 controls with GA confirmed from medical records (Figure 3).

The Arvo Ylppö Longitudinal Study

The Arvo Ylppö Longitudinal Study (AYLS) (Heinonen et al., 2008; Lano, 2002) is a cohort study of 2193 individuals born between 14.3.1985 and 15.3.1986 in the province of Uusimaa in Finland. The original study was carried out simultaneously in Uusimaa and in Bavaria, Germany (Bavarian Longitudinal Study) to examine the predictive value of standardized neurological examination performed by a paediatrician and to compare care and follow-up practices in Finland and Bavaria (Riegel, Ohrt, Wolke, & Österlund, 1995). The original cohort comprised 1) 1535 infants born alive and admitted to neonatal wards of the birth hospitals or transferred to the Neonatal Intensive Care Unit of the Hospital for Children and Adolescents in Helsinki within ten days of birth and 2) 658 controls not admitted to a neonatal ward and born after every second admitted infant in one of the three
largest maternity hospitals. Upon reaching adulthood they were invited to participate in a follow-up study. Clinical examination took place in Helsinki between in 2009–2012. Of the 1136 (51.8% of the original cohort) individuals who participated at the age of 25.2 years on average, we collected comprehensive data on maternal pregnancy and the peri- and neonatal period from hospital records, available for 899 participants. In the current work I will use data from 43 participants born early preterm, 118 participants born late preterm and 303 term-born participants belonging to the original control group with GA confirmed from medical records (Figure 3).

4.2.2 Perinatal and neonatal data

Perinatal and neonatal data was collected from the records of maternity welfare clinics and birth hospitals in both cohorts.

Gestational age

Gestational age was confirmed as accurately as possible by reviewing original hospital records. It was determined by ultrasonography in 747 cases, on the basis of the last menstrual period for 463 participants and according to a clinical decision in the birth hospital for two participants. According to GA at birth, we categorized the participants into three groups:

1. < 34 weeks of gestation (early preterm)
2. 34 to <37 weeks of gestation (late preterm) and
3. ≥37 weeks (controls).

Early life confounders

Maternal gestational disorders (maternal gestational diabetes, hypertension and preeclampsia) were defined by reviewing diagnoses from original hospital records. The diagnoses found were confirmed according to contemporary criteria (Miettola et al., 2013; Vääräsmäki et al., 2009). Birth weight SD scores were calculated according to Finnish birth weight standards (Pihkala, Hakala, Voutilainen, & Raivio, 1989). SGA was defined as more than two standard deviations below the mean for sex and length of gestation.
4.2.3 Clinical examination

The participants attended a clinical examination at mean ages of 23.3 (ESTER) and 25.3 (AYLS). In both studies, the study protocol included measurements of height, weight, waist circumference and body composition. Height was measured three times and the mean was calculated. BMI was calculated as weight/height² (kg/m²). Waist circumference was measured twice midway between the lowest rib and the iliac crest. Body composition was measured by using segmental multifrequency bioelectrical impedance analysis (BIA; InBody 3.0, Biospace Co., Ltd., Seoul, Korea).

4.2.4 The eating disorder inventory (III)

The Eating Disorder Inventory-2 (EDI-2) was developed for measurement of behavioural and psychological traits in anorexia nervosa (AN) and bulimia nervosa (BN) (Garner, Olmstead, & Polivy, 1983). To assess the symptoms and traits commonly associated with AN and BN we used three subscales of the inventory. These subscales, Drive for Thinness (7 items, Cronbach’s α for reliability in women 0.87, α for men 0.81), Body Dissatisfaction (8 items, α for women 0.90, α for men 0.85) and Bulimia (7 items, α for women 0.89, α for men 0.82), assess the attitudes towards weight, body shape and eating. Participants rated their response to each item on a 6-point Likert scale (ranging from “always” to “never”). We added the scores of the subscales together to form an EDI total score (22 items in total, α for women 0.93, α for men 0.90). Higher scores are indicative of more ED-related traits. The subscales we selected have been validated in Finnish women against DSM-IV diagnostic criteria (Keski-Rahkonen et al., 2006).

4.2.5 Food Frequency Questionnaire (IV)

To assess the usual diet, we used a validated semiquantitative 131-item food frequency questionnaire (FFQ) (Männistö, Virtanen, Mikkonen, & Pietinen, 1996). The FFQ used was designed to cover the whole diet over the preceding 12 months. In the FFQ form the participants indicated the frequency of consumption of each food item using nine frequency categories ranging from “never or seldom” to “six or more times per day”. Portion sizes were specified using commonly used units (e.g. slice, glass). The participants filled in the questionnaire at the study site after which a trained study nurse reviewed the questionnaire. The Finnish food
composition database, Fineli® (National Institute for Health and Welfare) (Reinivuo et al., 2010) was used to calculate the average daily intakes of energy, macronutrients and food groups.

To assess the overall quality of the diet, we used the Recommended Finnish Dietary Index (RDI) (Kanerva et al., 2013), which is based on the Finnish nutrition recommendations (National Nutrition Council, 2005). The index includes eight components which represent the average daily consumption of fruit; vegetables; rye; ratio of white meat to red and processed meat; ratio of polyunsaturated fatty acids to saturated fatty acids and trans-fatty acids; salt; sucrose and alcohol intake. The index was calculated according to the quartiles of consumption of each component in the control group. The overall index was formed by the sum of the points given (0–1 for alcohol, 0–3 for other items) and ranged from 0 to 24. A higher score indicates a healthier diet.

The total number of forms filled in the ESTER study was 737 and in the AYLS study, 465. We excluded forms that were filled incompletely (e.g., totally or partly empty questionnaires or the idea of the FFQ not understood) (ESTER n=24 [5 early preterm, 6 late preterm, 13 controls], AYLS n=4 [1 late preterm, 3 controls]) and used daily energy intake cut-off points of 0.5% at both ends of the daily energy intake distributions to exclude participants who reported the highest and lowest energy intakes. This was done for both sexes separately (ESTER n=7 [2 early preterm, 2 late preterm, 3 controls], AYLS n=2 [2 controls]). After exclusions, the sample size for the present study was 1165, comprising 182 participants born early preterm, 352 born late preterm and 631 term-born controls (Figure 3).

4.3 Ethics

HeSVA was approved by the Ethics Committee of the Department of Children’s and Adolescents’ Diseases and Psychiatry at the Helsinki University Central Hospital and the ESTER and AYLS studies were approved by the Coordinating Ethics Committee at Helsinki and Uusimaa Hospital District. All participants gave written informed consent in adult age in accordance with the Declaration of Helsinki.
Fig. 3. Flowchart of the study participants in the ESTER and AYLS studies (III and IV).
4.4 Statistical methods

**Study I:** From the data derived from the hospital records we calculated the mean intakes of energy, protein, fat and carbohydrate for the periods of 1-3 weeks, 4-6 weeks and 7-9 weeks. We used multiple linear regression analysis to assess associations between the mean energy and macronutrient intakes during the three 3-week periods as predictors and body composition measurements in young adulthood as outcomes. For the outcome variables with skewed distributions (BMI, lean body mass and REE) we used log-transformations of the distributions to attain normality. After analyses the results were back-transformed and are therefore expressed as percentages.

The covariates included in the adjusted models were: sex and age at the clinical examination (model 1), gestational age, birth weight SD score (model 2), highest parental education, and pregnancy and neonatal conditions: maternal smoking during pregnancy, maternal pre-eclampsia and neonatal exposure to ventilator treatment (days), bronchopulmonary dysplasia, septicaemia, exchange transfusion and persistent ductus arteriosus (full model). Finally the analyses were rerun with lifestyle factors (current smoking and leisure time physical activity) as covariates (model 4).

**Study II:** We used linear regression analysis to examine the relationships between early nutrition and early growth versus the main outcome variables, relative energy intake (the ratio of total energy intake to lean body mass (LBM)), relative REE (the ratio of REE to LBM), physical activity (MET) and the intake of macronutrients and foods. We used path analysis (described in detail in the appendix A in Study II) to further investigate the associations we found in multiple regression analyses between neonatal nutrition and growth versus adult outcomes ($p < 0.10$ in univariate regression model). All path models were based on a general hypothetical full-path model with the hypothesis that neonatal nutrition (total energy, protein, fat and carbohydrate intake) explains the levels of outcomes (relative energy intake or expenditure) and it may be partly mediated through neonatal growth during the same time period. The model uses all time points available for neonatal variables. All available data (no missing values) on dependent variables were included. Path analysis was performed with MPlus software (version 5.1, Muthén & Muthén, Los Angeles, CA, USA). Regression analyses and descriptive statistics were estimated using Stata (SE, version 14.1, StataCorp LLC, College Station, TX, USA).
The covariates included in the adjusted models were: sex and age at the clinical examination (model 1), gestational age, birth weight SD score (model 2), highest parental education, maternal smoking during pregnancy, maternal pre-eclampsia and neonatal exposure to ventilator treatment, bronchopulmonary dysplasia, sepsicaemia, exchange transfusion and persistent ductus arteriosus (model 3).

**Study III:** We compared descriptive characteristics of preterm and control participants using t tests for continuous variables and χ²-test for categorical variables. We then compared the differences in EDI-2 scores between preterm and term born groups by using linear regression analysis. As there was a statistically significant interaction between the effects of sex and gestational age (p for interaction <0.001) on EDI-2 scores, we conducted the analyses separately for men and women. Minor heterogeneity of study characteristics was accounted for by adjustment for cohort. Mean imputations were carried out for 39 women and 16 men with missing data on one EDI item and three women and five men with missing data on two EDI items. Covariates added to the regression models were highest parental education, birth weight SD score, maternal smoking during pregnancy, maternal pre-pregnancy BMI, primiparity and maternal gestational disorders (gestational hypertension, pre-eclampsia and gestational diabetes mellitus). We also adjusted for the subject’s current BMI and smoking.

**Study IV:** To compare descriptive characteristics of preterm and control participants we used t tests for continuous variables and χ²-tests for categorical variables. We then examined the associations between preterm birth and food and nutrient intake in adulthood by linear regression analysis. We performed log-transformations of variables concerning food intake because of non-normal data and the presence of zero values. Therefore, we report mean differences in food intake as back-transformed percentages. All regression models included age and recruitment cohort. All models concerning intakes of food as well as RDI and its components, also included total energy intake as a covariate. Model 2, in addition to previously mentioned variables, included highest parental education, maternal BMI before pregnancy, birth weight SD score, maternal smoking during pregnancy, gestational hypertension, pre-eclampsia and gestational diabetes mellitus. Model 3, in addition to previously mentioned variables, included current characteristics of the participant, BMI, living at parental home and daily smoking.

A two-tailed p value <0.05 was considered statistically significant throughout the analyses and all statistical analyses were performed with SPSS for Windows, Versions 21.0–23.0 unless otherwise stated.
5 Results

The results of the current work are presented in order of the aims of the study. Results concerning the role of early nutrition of VLBW adults in programming of adult health are reported first, followed by results concerning preterm birth, and body image and food and nutrient intake in adulthood.

5.1 Early nutrition of young adults born at very low birth weight (I, II)

The mean gestational age of the VLBW participants at birth (n=127) was 29.0 (SD 2.1) weeks, mean birth weight 1105 (218) gr and mean birth weight SD score -1.20 (1.51). Thirty-seven (29%) participants were born SGA and 23 (18%) from a pregnancy complicated by maternal pre-eclampsia. The mean duration of supplemental oxygen during the neonatal weeks was 15 (25th, 75th percentile 4, 35) days and that of mechanical ventilation six (0, 17) days. Bronchopulmonary dysplasia, prospectively confirmed by a neonatologist, was diagnosed with 24 (19%) infants and sepsis with eight (6%) infants. The mean weight SD score at term age was -2.51 (SD 1.16).

The mean energy and protein intakes during the first three weeks of life of the VLBW participants were well below the current recommendations (Table 4). Energy intake slowly reached the current recommended level in later weeks but protein intake remained at the lower level throughout the study period of the first nine weeks of life. Mean fat and carbohydrate intakes were close to or at the recommended levels.

Table 4. Mean intakes (SD) of energy and macronutrients during the first nine weeks of life among the young adults born at VLBW and current recommendations for enteral intake (Agostoni et al., 2010)

<table>
<thead>
<tr>
<th>Time</th>
<th>Energy (kcal/kg/d)</th>
<th>Protein (g/kg/d)</th>
<th>Fat (g/kg/d)</th>
<th>Carbohydrate (g/kg/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weeks 1-3</td>
<td>94.1 (15.5)</td>
<td>1.4 (0.4)</td>
<td>4.3 (1.1)</td>
<td>11.1 (1.29)</td>
</tr>
<tr>
<td>Weeks 4-6</td>
<td>119 (14.6)</td>
<td>1.9 (0.4)</td>
<td>5.9 (1.0)</td>
<td>12.4 (1.30)</td>
</tr>
<tr>
<td>Weeks 7-9</td>
<td>124 (13.3)</td>
<td>2.1 (0.5)</td>
<td>6.1 (0.9)</td>
<td>12.9 (1.28)</td>
</tr>
<tr>
<td>Current</td>
<td>110-135</td>
<td>&lt;1000g: 4.0-4.5</td>
<td>4.8-6.6</td>
<td>11.6-13.2</td>
</tr>
<tr>
<td>recommendations</td>
<td>1000-1800g: 3.5-4.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
5.1.1 The association between infant feeding and body composition in young adult age (I)

As expected, VLBW men and women differed in body composition measurements in young adult age. Interaction between sex and early nutritional intake was not statistically significant, however, so we did not perform sex-specific analyses. Early nutrition during the first three weeks of life was associated with body composition in adult age. There was no association from the 4th week onwards (study I). 10 kcal/kg/day higher energy and 1g/kg/day higher protein intakes during the first three weeks of life predicted higher BMI (energy 2.12%; 95% CI 0.30, 3.87) (protein 7.36%; -0.40, 15.8) and higher lean body mass (energy 2.33%; 0.70, 3.98) (protein 11.2%; 3.77, 19.1) at young adult age, but were not associated with height, percentage body fat or waist circumference (Figure 4 and Table 3 in study I). The association found with LBM survived adjustments for sex, age at the clinical examination, gestational age at birth, birthweight SD score, parental education and pre- and neonatal factors. When current smoking and leisure time physical activity were added to the model, the results remained similar.

1g/kg/day higher fat intake predicted higher BMI (3.77%; 1.20, 6.29) and higher LBM (3.56%; 1.21, 5.97) in adult age. These associations were present after adjustments for all included covariates. Higher fat intake also tended to be associated with higher body fat percentage (0.85; -0.11, 1.81) and larger waist circumference (1.41cm; -0.12, 2.94), however, adjustments for neonatal and current characteristics attenuated these results.

Carbohydrate intake during the first weeks of life did not predict any of the outcomes assessed in this study.
Fig. 4. Nutritional intake during the first three weeks of life and measurements of body composition in young adulthood adjusted for sex and age at the clinical examination. Error bars present the non-standardized regression coefficient with 95% CI. Log transformed values were used for BMI and LBM in the analyses and therefore the values presented are expressed as back-transformed percentages. Abbreviations: BMI, body mass index, LBM, lean body mass, PBF, percentage body fat.

5.1.2 The association between infant feeding and resting energy expenditure in adult age (I)

Higher energy, protein and fat intakes during the first three weeks of life were associated with lower ratios of REE to LBM and tended to be associated with higher REE (Table 5). These associations mainly survived adjustments for gestational age at birth, birth weight SD score and pre-and neonatal characteristics, but became attenuated after adjustments for current lifestyle of the participant; leisure time physical activity and smoking.
Table 5. The association between nutrition during the first three weeks of life and resting energy expenditure (REE) and the REE to lean body mass (LBM) ratio in adulthood.

<table>
<thead>
<tr>
<th>Infant feeding</th>
<th>REE (%) (n=96)</th>
<th>B (95% CI)</th>
<th>P</th>
<th>REE/LBM (%) (n=92)</th>
<th>B (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy (10 kcal/kg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.34 (-0.43 to 3.14)</td>
<td>0.13</td>
<td>-1.35 (-2.46 to -0.22)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>1.82 (0.00 to 3.87)</td>
<td>0.05</td>
<td>-1.15 (-2.28 to -0.01)</td>
<td>0.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>1.91 (-0.18 to 4.06)</td>
<td>0.07</td>
<td>-1.02 (-2.33 to 0.31)</td>
<td>0.13</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>2.13 (0.03 to 4.28)</td>
<td>0.05</td>
<td>-1.11 (-2.43 to 0.22)</td>
<td>0.10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protein (g/kg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>7.02 (-0.86 to 15.5)</td>
<td>0.08</td>
<td>-6.46 (-11.0 to -1.74)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>8.52 (0.16 to 17.0)</td>
<td>0.05</td>
<td>-5.52 (-10.0 to -0.81)</td>
<td>0.02</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>8.53 (-0.18 to 18.0)</td>
<td>0.05</td>
<td>-4.73 (-9.72 to 0.52)</td>
<td>0.08</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>9.03 (0.30 to 18.5)</td>
<td>0.04</td>
<td>-4.88 (-9.85 to 0.38)</td>
<td>0.07</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fat (g/kg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>2.41 (-0.18 to 5.07)</td>
<td>0.07</td>
<td>-2.08 (-3.69 to -0.44)</td>
<td>0.01</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>2.89 (0.23 to 5.62)</td>
<td>0.03</td>
<td>-1.70 (-3.32 to -0.05)</td>
<td>0.04</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>3.13 (0.14 to 6.21)</td>
<td>0.04</td>
<td>-1.50 (-3.35 to 0.39)</td>
<td>0.12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>3.39 (0.41 to 6.46)</td>
<td>0.03</td>
<td>-1.64 (-3.48 to 0.24)</td>
<td>0.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbohydrate (g/kg/d)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 1</td>
<td>1.21 (-0.93 to 3.23)</td>
<td>0.28</td>
<td>-0.28 (-1.63 to 1.08)</td>
<td>0.68</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 2</td>
<td>1.53 (-0.57 to 3.68)</td>
<td>0.15</td>
<td>-0.41 (-1.73 to 0.93)</td>
<td>0.55</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 3</td>
<td>1.29 (-0.93 to 3.56)</td>
<td>0.25</td>
<td>-0.10 (-1.53 to 1.36)</td>
<td>0.89</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Model 4</td>
<td>1.52 (-0.72 to 3.81)</td>
<td>0.18</td>
<td>-0.12 (-1.58 to 1.36)</td>
<td>0.87</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Adjusted models are: Model 1, adjusted for sex and age at the clinical examination; Model 2 adjusted for variables in Model 1 + gestational age and birthweight SD score; Model 3 adjusted for variables in Model 2 + highest parental education, maternal smoking during pregnancy, and maternal preeclampsia and for neonatal exposures of treatment with ventilator (days), bronchopulmonary dysplasia, sepsisemia, exchange transfusion, or persistent ductus arteriosus; Model 4 adjusted for variables in Model 3 + leisure time exercise and current daily smoking.

5.1.3 The association between infant feeding and food and nutrient intake and physical activity in adulthood (II)

When self-reported physical activity and intake of food items assessed by 3-day food record were examined as outcomes, there were no statistically significant associations with early nutrition. Adjustments for potential early-life confounders or current mediating characteristics did not change the results (study II).
5.1.4 The association between infant feeding and growth and energy metabolism in adulthood (II)

To describe energy metabolism at an adult age we used two main outcome variables in our path analysis, i.e. the relationship between total energy intake and LBM (relative energy intake), and the relationship between REE and LBM (relative REE). Higher energy intake during the first three weeks of life predicted both, lower relative total energy intake and lower relative REE (Table 6). Adjustments for potential early-life confounders did not change the results, with the exception that adjustment for neonatal factors (treatment with ventilator, BPD, septicemia, exchange transfusion and PDA) strengthened the association with total relative energy intake. Higher protein and fat intakes during the first three weeks of life were associated with lower relative REE in all models and also with lower relative total energy intake when fully adjusted for confounding factors. There were no statistically significant associations from the 4th week onwards.

Table 6. Path coefficients and 95% bias-corrected confidence intervals for models assessing the infant feeding and the relative energy intake and relative resting energy expenditure in adult age.

<table>
<thead>
<tr>
<th>Infant feeding</th>
<th>Relative energy intake</th>
<th>Relative resting energy expenditure</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Model 1</td>
<td>Full Model2</td>
</tr>
<tr>
<td></td>
<td>Path coefficient</td>
<td>Path coefficient</td>
</tr>
<tr>
<td></td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Mean energy intake (10kcal/kg/d)</td>
<td>-1.4 (-2.9; -0.1)</td>
<td>-2.7 (-4.4; -1.0)</td>
</tr>
<tr>
<td>Mean protein intake (g/kg/day)</td>
<td>-4.7 (-12.4; 1.5)</td>
<td>-8.1 (-16.5; -0.3)</td>
</tr>
<tr>
<td>Mean fat intake (g/kg/day)</td>
<td>-1.8 (-4.1; 0.2)</td>
<td>-3.3 (-6.0; -0.8)</td>
</tr>
</tbody>
</table>

Model 1, Adjusted for birthweight SD score, sex and age at clinical examination.
Full Model, adjusted in addition for gestational age at birth, highest parental education, maternal smoking during pregnancy, maternal pre-eclampsia, ventilator treatment (days), bronchopulmonary dysplasia, septicemia, exchange transfusion and persistent ductus arteriosus.

Path analysis (described in Study II) revealed that concerning relative energy intake the total effects were mostly explained by the direct effects of early nutrition (Table 7). A path mediated by early growth was present but reached statistical significance only with protein intake. Regarding relative REE, indirect effects were not found.
Table 7. Model derived effect estimates with 95% bias-corrected confidence intervals for relative energy intake at an adult age.

<table>
<thead>
<tr>
<th>Infant feeding</th>
<th>Direct effect: Estimate (95%CI)</th>
<th>Indirect effect: Estimate (95%CI)</th>
<th>Total effect: Estimate (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean energy intake (10kcal/kg/d)</td>
<td>-2.14 (-3.77; -0.62)</td>
<td>-0.37 (-1.02; 0.03)</td>
<td>-2.51 (-3.92; -1.06)</td>
</tr>
<tr>
<td>Mean protein intake (g/kg/d)</td>
<td>-5.96 (-12.44; -0.59)</td>
<td>-1.73 (-4.65; -0.09)</td>
<td>-7.68 (-13.60; -2.12)</td>
</tr>
<tr>
<td>Mean fat intake (g/kg/d)</td>
<td>-2.45 (-4.81; -0.33)</td>
<td>-0.54 (-1.36; 0.01)</td>
<td>-2.98 (-5.24; -0.81)</td>
</tr>
</tbody>
</table>

5.2 Preterm birth and adult outcomes (III, IV)

The perinatal and neonatal characteristics of the participants from the ESTER- and AYLS-cohorts are presented in Table 8. Participants of the preterm groups in both cohorts were more often twins or SGA. They were also more likely to be born from pre-eclamptic pregnancy. Preterm-born participants were younger than controls, mainly due to differences in original cohort designs. In adult life women born early preterm had a higher body fat percentage than term-born women. Further, those born preterm were living at their parental home more often.

As the differences between the preterm groups and controls were similar in both cohorts (p for interaction > 0.05), we report the results pooled, separately for both sexes (interaction for sex p < 0.001).
Table 8. Characteristics of the participants from ESTER and AYLS cohorts included in Studies III and IV

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Early Preterm n=191</th>
<th>Late Preterm n=364</th>
<th>Controls n=657</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ester</td>
<td>148 (77.5)</td>
<td>246 (67.6)</td>
<td>354 (53.9)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Women</td>
<td>98 (51.3)</td>
<td>182 (50.0)</td>
<td>350 (53.3)</td>
<td>0/0/0</td>
</tr>
<tr>
<td><strong>PRENATAL CHARACTERISTICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maternal hypertension</td>
<td>25 (13.1)</td>
<td>47 (12.9)</td>
<td>77 (11.7)</td>
<td>4/15/25</td>
</tr>
<tr>
<td>Maternal pre-eclampsia</td>
<td>41 (21.5)</td>
<td>47 (12.9)</td>
<td>20 (3.0)</td>
<td>4/15/25</td>
</tr>
<tr>
<td>Maternal GDM</td>
<td>4 (2.1)</td>
<td>15 (4.1)</td>
<td>16 (2.4)</td>
<td>22/24/9</td>
</tr>
<tr>
<td>Maternal smoking during pregnancy</td>
<td>37 (20.1)</td>
<td>72 (20.1)</td>
<td>106 (16.3)</td>
<td>7/6/7</td>
</tr>
<tr>
<td><strong>BIRTH CHARACTERISTICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SGA</td>
<td>34 (17.8)</td>
<td>52 (14.3)</td>
<td>10 (1.5)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Birthweight</td>
<td>1736 (487)</td>
<td>2884 (536)</td>
<td>3596 (484)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Birthweight SD</td>
<td>-.74 (1.4)</td>
<td>-.59 (1.3)</td>
<td>.03 (.98)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Gestational age</td>
<td>31.6 (2.2)</td>
<td>35.8 (.78)</td>
<td>40.1 (1.2)</td>
<td>0/0/0</td>
</tr>
<tr>
<td><strong>CLINICAL CHARACTERISTICS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age at clinical examination</td>
<td>23.6 (1.6)</td>
<td>23.8 (1.5)</td>
<td>24.4 (1.3)</td>
<td>0/0/0</td>
</tr>
<tr>
<td>Daily smoking</td>
<td>52 (7.4)</td>
<td>94 (6.2)</td>
<td>175 (6.9)</td>
<td>1/5/6</td>
</tr>
</tbody>
</table>

P values for the differences between each preterm born group and controls examined by t test in continuous and χ²-test in categorical variables

Abbreviations: GDM Gestational Diabetes Mellitus, SD Standard Deviation; SGA Small for Gestational Age

5.2.1 Body image (III)

Totals of 145 participants born early preterm, 238 participants born late preterm and 347 term-born control participants filled in the Eating Disorder Inventory (EDI-2) questionnaire during the clinical visit. Mean scores from the inventory are presented in Table 9.
Table 9. Eating Disorder Inventory (EDI-2) and subscale scores in preterm groups* and controls, mean (SD).

<table>
<thead>
<tr>
<th>EDI score</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Early Preterm</td>
<td>Late preterm</td>
</tr>
<tr>
<td></td>
<td>n=97</td>
<td>n=175</td>
</tr>
<tr>
<td>EDI sum</td>
<td>64.1 (7.1)**</td>
<td>67.9 (16.8)</td>
</tr>
<tr>
<td>Drive for Thinness</td>
<td>22.3 (7.0)**</td>
<td>23.8 (6.8)</td>
</tr>
<tr>
<td>Body Dissatisfaction</td>
<td>24.8 (7.7)**</td>
<td>26.2 (7.9)</td>
</tr>
<tr>
<td>Bulimia</td>
<td>17.3 (6.1)</td>
<td>17.9 (4.9)</td>
</tr>
</tbody>
</table>

*Early Preterm, <34 weeks of gestational age; Late preterm 34-<37 weeks of gestational age, ** p < 0.01 for difference between early preterm born group and controls.

When compared with control women born at term, women born early preterm scored lower in summed EDI scores (mean difference 4.1 points [95% CI -8.0,-0.2, \( p = 0.04 \) adjusted for age and cohort). The difference remained similar after further adjustments for socioeconomic status and peri- and neonatal characteristics, and further increased when also adjusted for the current characteristics of the participant (mean difference -5.3 [95% CI -8.9, -1.7], \( p = 0.004 \)). We did not observe a statistically significant difference between women born late preterm and controls or men born early or late preterm and controls in any of the adjusted models (Figure 5 and Study III).

When the subscale scores (Drive for Thinness, Body Dissatisfaction, Bulimia) were assessed separately, young women born early preterm scored statistically significantly lower in both, Drive for Thinness (\( p = 0.03 \)) and Body Dissatisfaction (\( p = 0.02 \)) (Study III, table 3). The difference remained similar or further increased after adjustments.

However in the Bulimia subscale, we saw no difference between the early-preterm-born women and controls.

There were no differences between women born late preterm and controls or men born preterm and controls in unadjusted or adjusted models.
Fig. 5. Mean differences and 95% confidence intervals (error bars) in EDI sum scores in young adults born early and late preterm compared with controls born at term adjusted for age, cohort, highest parental education, maternal smoking during pregnancy, maternal pre-pregnancy BMI, birthweight SD score, primiparity, maternal pregnancy disorders, BMI and daily smoking of the participant.

Sensitivity analyses

The exclusion of participants with major mental or physical impairments (CP, mental disability and/or other severe physical disability) did not change our results in EDI sum scores or any of the subscale scores alone. Exclusion of participants with a Beck Depression Inventory (BDI) score greater than 10 (controls n=112 / early preterm n=29 / late preterm n=54) or missing BDI values did not affect the results among men. Among women however, the differences between preterm groups and controls in EDI sum scores as well as in subscale scores separately were strengthened, and becoming statistically significant in the late preterm group also. The results were similar in Drive for Thinness- and Body Dissatisfaction-subscales.
5.2.2 Food and nutrient intake in adulthood (IV)

Differences in food and nutrient intake in adulthood were examined by assessing the differences in macronutrient intake, and adherence to the recommended diet and by looking more closely at previously found differences in the intake of certain food items between preterm-born individuals and term born controls.

Macronutrient intakes

Total energy intake at an adult age, as well as energy intakes from carbohydrates, fat and protein, were similar in preterm-born groups and controls. Adjustments for the main confounders, parental education, prenatal characteristics and current BMI, smoking and living at parental home, did not change the results (Table 10). Energy from alcohol was lower in women born early preterm \((p < 0.05\) in all models) when compared with term-born controls. Men born early preterm also consumed less alcohol when compared with controls, although this difference was not statistically significant.

Table 10. Linear regression models showing differences (95% CIs) in intake of macronutrients between the preterm groups and controls.

<table>
<thead>
<tr>
<th>Nutritional intake</th>
<th>Men</th>
<th></th>
<th></th>
<th>Women</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Controls</td>
<td>Early Preterm</td>
<td>Late preterm</td>
<td>Controls</td>
<td>Early Preterm</td>
<td>Late Preterm</td>
</tr>
<tr>
<td></td>
<td>n=293</td>
<td>n=87</td>
<td>n=175</td>
<td>n=338</td>
<td>n=95</td>
<td>n=177</td>
</tr>
<tr>
<td>Energy (kcal/day)</td>
<td>Mean</td>
<td>B (95% CI)</td>
<td>B (95% CI)</td>
<td>Mean</td>
<td>B (95% CI)</td>
<td>B (95% CI)</td>
</tr>
<tr>
<td>Carbohydrate (E%/day)</td>
<td>2540</td>
<td>3.2(-241.5; 247.8)</td>
<td>-55.1(-246.7; 136.5)</td>
<td>1880</td>
<td>-57.3(-209.8; 95.2)</td>
<td>83.3(-30.7; 197.4)</td>
</tr>
<tr>
<td>Fat (E%/day)</td>
<td>44.1</td>
<td>0.5 (-1.1; 2.0)</td>
<td>0.0 (-1.2; 1.2)</td>
<td>47.2</td>
<td>0.0 (-1.9; 1.8)</td>
<td>0.0 (-1.3; 1.4)</td>
</tr>
<tr>
<td>Protein (E%/day)</td>
<td>33.7</td>
<td>0.4 (-0.8; 1.7)</td>
<td>0.5 (-0.5; 1.5)</td>
<td>32.9</td>
<td>0.4 (-1.1; 1.8)</td>
<td>-0.2 (-1.2; 0.9)</td>
</tr>
<tr>
<td>Alcohol (E%/day)</td>
<td>18.7</td>
<td>-0.3 (-1.1; 0.5)</td>
<td>0.0 (-0.6; 0.6)</td>
<td>17.9</td>
<td>0.5 (-0.2; 1.2)</td>
<td>0.3 (-0.2; 0.8)</td>
</tr>
</tbody>
</table>

Abbreviations: CI, confidence interval; E%, percentage of total energy intake
Adherence to recommended diet

Young women born early preterm scored 0.77 units (95% CI 0.03, 1.51) lower in recommended dietary index than peers born at term (mean score 10.5, SD 2.9) when adjusted for sex, age, parental education and early life confounders (Figure 6) (Study IV, table 3). This indicates a slightly lower overall quality of diet. Adjustment for current mediating characteristics attenuated the difference. When the lower intake of alcohol was included in the total index, women born early preterm tended to score lower (mean difference -0.74 [95% CI -1.50, 0.02]) than term born peers. We observed no difference in scores between women born late preterm (mean difference 0.04 [95% CI -0.52, 0.59]) and controls or scores in men born preterm (early preterm -0.37 [95% CI -1.15, 0.40], late preterm -0.01 [95% CI -0.62, 0.60]) and their controls (mean 10.5, SD 3.0).

When the different components of the recommended dietary index were assessed separately (Study IV, Supplemental Table S1), it was found that the ratio of red meat to white meat was higher in women born early preterm when compared with controls. On the other hand, alcohol consumption within this group was lower. Men born early preterm consumed less fruit and berries when compared with controls. At the same time the ratio of red meat to white meat was lower in this group. There were no differences between the late-preterm group and controls (women or men). We observed no differences between preterm-born groups and controls in other components of the index.

Replication of previous findings related to food items

The differences regarding specific food items that have been previously described in adults born at VLBW and controls were also assessed more specifically (data not shown). There was a statistically significant difference in the consumption of fruits and berries between the preterm-born participants and controls such that women born early preterm consumed more and men born early preterm consumed less fruits and berries when compared with respective controls. Among men, this difference survived adjustments for confounding factors. In women the difference became attenuated after additional adjustments for prenatal and current lifestyle factors. We observed no difference between the groups in the intake of vegetables or milk products. Among early preterm women the intake of milk products was slightly higher than in controls.
Fig. 6. Mean differences and 95% confidence intervals (error bars) in the recommended dietary index in young adults born early and late preterm compared with controls born at term. (Data adjusted for sex, age, parental education and early life confounders.)

Women born early preterm consumed less fat. This was particularly seen in the low-fat margarines but not in the intakes of butter or oil. Among men, participants born early preterm consumed more margarines, but the difference was of borderline statistical significance.

Women and men born early preterm consumed fewer sweets when compared with respective controls. This difference was seen more clearly among men and was also present in the late preterm born group. In women the difference was not seen after adjustments for prenatal and current characteristics.
6 Discussion

This doctoral thesis describes the associations between nutrition during the early weeks after preterm birth at VLBW and body composition and energy metabolism at an adult age, and associations between preterm birth and traits related to eating disorders and food and nutrient intake in adulthood. The information is based on three cohort studies; the Helsinki Study of Very Low Birth Weight Adults, the ESTER Preterm birth study and the Arvo Ylppö Longitudinal Study.

6.1 Early nutrition of young adults born at very low birth weight

In this work it was found that macronutrient intake during the first three weeks after preterm birth at VLBW predicted body composition and energy metabolism twenty years later (Studies I and II). However, early nutrition was unrelated to the amount of physical activity or to diet and food preferences as assessed by consumption of a variety of food items (Study II).

Regarding early nutrition, early protein intake in particular has attracted discussion lately. The early protein hypothesis suggests that in term born infants, higher protein intake in infancy, resulting in faster growth, is associated with overweight and obesity in later life (Koletzko et al., 2005). This hypothesis has gained support from studies in which infants have been assigned to receive either standard or nutrient-enriched formula. In a study including two cohorts of infants born at term but SGA, fat mass was 22–38% greater in children who were randomly assigned to receive the nutrient-enriched formula (1.8–2.0g/100ml) in infancy when compared with those who received standard formula (1.4 g/100ml) (Singhal et al., 2010). The finding was replicated in the EU Childhood Obesity Project, in which BMI was significantly higher in the group receiving high-protein formula when compared with the group receiving lower-protein formula (difference of 0.51 kg/m2; 95% CI: 0.13, 0.90; p= 0.009) at six years age (Weber et al., 2014). In that study, protein intake was on average 1 g/kg higher in the group receiving high-protein formula at three months of age when compared with those receiving low-protein formulas. In our study, however, at relatively low protein intake levels, higher protein intake during the first three weeks of life was associated with higher lean body mass whereas no association was found between early protein intake and BMI or body fat percentage in adulthood.

When comparing the results it should firstly be emphasized that the previous protein trials have included term-born infants. Secondly, the protein intake in our
study population (1.4 [SD 0.4] g/kg/day) was well below the current recommendations (~4.0 g/kg/day). The recommended protein intake for preterm-born infants in the 1980’s was close to the currently recommended levels (3.5–4.0 g/kg/day) (American Academy of Pediatrics, 1985). The recommendations for term-born infants, however, are considerably lower today (1.99 g/kg/day) than in the 1980’s (2.25–3.0 g/kg/day) (World Health Organization, 1985). The estimated amount of protein received from mothers’ milk is 2.09 g/kg/day (Räihä, 1994) and that from standard infant formula is 3.2–4.2 g/kg/day (Fenton, Premji, Al-Wassia, & Sauve, 2014).

Our results could imply that the association between early protein intake and adult body composition is non-linear. At relatively low intake levels, the higher early protein intake predicts higher LBM whereas at adequate or high levels, according to previous studies, higher intake might be predictive of an increased risk of obesity. When interpreting these results, the timing of the exposure also needs to be taken in account. The infants in our study were born preterm, at the time when growth in utero is fast with continuous maternal protein supply. It has been suggested that in the healthy fetus, daily fetal protein intake increases from 1.25 g/kg/day in 24th gestational week up to 4.34 g/kg/day at the end of the 3rd trimester of pregnancy (Ziegler, O’Donnell, Nelson, Fomon, 1976). This supply is discontinued when the infant is born prematurely. It is common, that early nutrition of the preterm-born infant does not succeed in reaching the level of maternal nutritional supply via placenta. Consequently, the growth of the new-born infant is compromised. In these infants, the higher early protein intake may have resulted in healthier body composition in adult age by reducing the early catabolic state, which has been suggested to affect later growth trajectories (Hay, 2008).

We found that higher nutritional intake during the first three weeks of life, especially the intake of protein, was associated with higher REE but a lower REE/LBM ratio at a young adult age (I). The association between early protein intake and lower REE/LBM was accompanied by an association with lower energy intake per kg LBM, which was partly mediated by early growth (II). Past studies have shown that although adults born preterm or at LBW have lower REE and lower LBM than their peers born at term, they have higher REE per unit LBM (Eriksson et al., 2002; Sipola-Leppänen et al., 2011). These results together show that those receiving higher amounts of protein at an early age, are metabolically less active, and this is accompanied by lower energy intake per kg of body weight (II). This may be a consequence of metabolically less active organs. A theory suggesting that the metabolic adaptations caused by fetal malnutrition and followed
by a more abundant postnatal environment predispose an individual to altered metabolic features and an increased risk of metabolic syndrome is included in DOHaD (Hanson & Gluckman, 2014). Our results are in line with this theory, as a low early intake of protein is associated with more active energy metabolism in adult life.

We were the first to include early growth in analyses of the association between early nutrition and energy metabolism. The results suggested that the association between early nutrition and energy metabolism in adulthood is only partly mediated by early growth. Rapid weight gain in infancy has been consistently linked to increased incidences of obesity in later life (Baird et al., 2005; Monteiro & Victora, 2005) and catch-up growth early in life has been listed as one risk factor of later obesity. Past studies have not been able to differentiate between the effects of nutrition and growth. In our study, nutrient intakes were low during the first weeks of life. Consequently, the growth of VLBW infants was very slow when compared with growth in utero. In this context, early nutrition had an independent role in predicting adult outcomes.

6.2 Programming of food preferences

The association between early-life exposures and adult-age diet and food preferences was examined in Studies II and IV. In Study II, we found no association between early nutrition and intakes of food items or macronutrients at an adult age, suggesting that the associations between neonatal nutrient intake and adult energy balance are unlikely to be mediated through specific food preferences. One consistent finding in experimental animal studies on programming of food and nutrient intake is that malnourishment during the early stages of life is associated with the intake of more palatable and more energy-dense foods at an adult age; in humans this was shown in the Dutch Famine Study (Lussana et al., 2008; Stein et al., 2009), and this was also our hypothesis. As total energy intake is fairly well regulated by physiological mechanisms and thus shows little day-to-day variation, it is of note that although we found no associations between early nutrition and the intakes of various food items in later life, higher energy intake during the first three weeks of life was associated with lower total energy intake at an adult age; a finding that is consistent with the theory suggesting that malnourishment during early stages of life is associated with higher energy intake in later life.

In study IV food and nutrient intake in young adults born early and late preterm were examined. Young women born early preterm had a poorer adherence to
nutritional recommendations when compared with term-born controls. There were
no differences in food preferences or adherence to nutritional recommendations in
women born late preterm versus controls. In men, those born early preterm
consumed less fruit and berries, consistent with the results of previous studies
(Kaseva et al., 2013). However, there was no difference in adherence to nutritional
recommendations among men. Some differences were opposite among women and
men regarding the intake of various food items. Women born early preterm showed
a higher intake of fruits and berries when compared with term-born women,
whereas in men the difference was in the opposite direction. Against our hypothesis,
the overall consumption of more palatable foods, i.e. those rich in sugar or fats did
not differ between the groups. Neither did we observe any difference in the
consumption of milk products, which has been reported in previous studies (Kaseva
et al., 2013), between the preterm-born groups and controls.

Although increased appetite or preference for more palatable food induced by
altered early experiences may be one mechanism in increasing metabolic risks in
later life, the results of our study did not fully follow this theory. Our findings,
however, suggest that especially young women born at the lowest range of
gestational age, in particular, do show reduced adherence to the recommended diet
and might therefore benefit from more detailed dietary counselling already in
childhood. It should be emphasized, however, that past studies have involved the
use of various methods for assessing food intake which may cause inconsistency in
the results. The cohorts studied in connection with the developmental origins of
food preferences differ as regards the age of participants as well as the early
exposures. In a recent review it was suggested that associations between early
exposures and feeding behaviour in later life might depend on the type of early
insult (Portella et al., 2012). As the development of food preferences begins in early
gestation and is a continuous process until adulthood, the differences found in our
study may develop further as the study participants become older.

6.3 Preterm birth and body image in adulthood

The results from Study III were also confined to women born early preterm as we
found that young women born early preterm have fewer symptoms related to EDs
than women born at term or women born late preterm. Among men, we found no
differences between the preterm and term born groups. The results of our study
indicate that young women born early preterm actually have a healthier body image
when compared with term-born peers, in contrast to the findings of some previous
studies suggesting that individuals born preterm have an increased risk of EDs (Cnattingius et al., 1999; Favaro et al., 2006; Foley et al., 2001; Goodman et al., 2014; Lindberg & Hjern, 2003). Results similar to ours were found in another study involving the same EDI-2 scales, showing that women born preterm at VLBW have lower levels of ED-related symptoms than their peers born at term (Wehkalampi et al., 2010). When we excluded the participants with depressive symptoms as assessed by using the Beck Depression Inventory, a healthier body image was also seen in young women born late preterm. The reasons for the differences between our results and those suggesting a higher risk of EDs in preterm-born individuals are not clear. We have suggested that possibly the traits that are measured by the EDI scales we used have a smaller role in the aetiology of EDs in preterm-born individuals than in the general population (Matinolli et al., 2016).

Past studies concerning the association between early life exposures and eating disorders have been focused either on ED symptomatology or ED diagnoses. The study designs also vary from population-based case-control designs to cohort studies (Table 3). In a recent meta-analysis of obstetric risk factors of EDs a non-significant effect of prematurity on eating disorders was found. However, only six of 14 studies concerned were included in the final analyses as a result of differing study designs. Publication bias was also suggested and variability in the studies included remained relatively great (Krug et al., 2013). As pointed out by Garner and colleagues (Garner et al., 1983), EDI-2 should not be used in screening for or diagnosing AN. There are no published data that would enable us to directly quantify the difference we observed in terms of the risk of manifest EDs.

In addition to an altered body image, eating disorders are characterized by a distorted view of food. Past research has shown consistent links between very strict dietary control and disordered eating (Linardon & Mitchell, 2017; Timko & Perone, 2005). In our study cohorts the young women born early preterm, in addition to a healthier body image, also showed lower adherence to recommended eating guidelines. There might be some shared underlying mechanisms behind these results such as factors related to social or behavioural influences.

### 6.4 Possible mechanisms

The precise mechanisms acting behind the associations found in this study are unknown, but past studies have suggested many possible scenarios. The theory behind the concept of programming suggests that exposures in utero and during early postnatal development may permanently change organ development at the
time when the organism is most vulnerable such insults (Koletzko et al., 2011). Furthermore, the hypothalamic-pituitary-adrenal (HPA) axis, also known as the “stress axis” plays a role in regulating energy expenditure and energy storage. It has also been proposed to play a role in the development of food preferences. Functioning of the HPA axis is set early in life and is affected by early stress and nutritional insults. (Gali Ramamoorthy, Begum, Harno, & White, 2015; Reynolds et al., 2015) Previous investigators have reported lower cortisol responses, as well as a blunted HPA-axis response to stress, in adults born preterm (Buske-Kirschbaum et al., 2007; Kaseva et al., 2014). It would be interesting to examine the role of the HPA axis in relation to our findings.

In addition to biological mechanisms, other possible mechanisms underlying the associations we observed include sociodemographic and behavioural influences. Sociodemographic factors affect eating habits, the risk of eating disorders and also body size and composition. In our study, the results persisted after controlling for age and parental education. There are also several social and behavioural factors influencing the outcomes we were interested in. For example peer victimization (Nadeau, Tessier, Lefebvre, & Robaey, 2004) and the parent-child relationship (Jaekel, Wolke & Chernova, 2012; Pyhälä et al., 2011) have been shown to differ in between those born preterm versus controls.

6.5 Strengths and limitations

The data in this work were derived from three population-based cohort studies with details of early-life exposures and a wide range of potential confounders. Although associations between certain early-life events and outcomes at an adult age were found, issues with cohort selection and problems with controlling for confounding are always present. Despite high-quality data and careful analyses, there are several potential limitations in our study.

The data on infant feeding used in Studies I and II is unique, with objective recordings by medical staff. However, the historical perspective also brings some limitations. We were not able to trace the exact compositions of all nutritional products, and had to use compositions of corresponding products instead. The nutritional composition of breast milk is also hard to define, although we have used the best available data in assessing it. It is also of note that the nutrient intakes especially that of protein, were well below the current recommendations and were accompanied by much slower growth than would have been expected in utero or in VLBW infants receiving adequate care today. The sample size was relatively small,
as we were not able to find the hospital records for 25 study participants. The non-participant analysis showed that those with no available data were on average born at a greater gestational age and were also discharged earlier from hospital. The women with no data were taller and as a consequence had a greater LBM (Study I, supplemental table 1). It is possible that the participants excluded from our analyses represent those with greater early macronutrient intakes. This would, however, be consistent with our suggestion that the relationship between early protein intake and lean body mass in adult life is a characteristic of those with low early protein intake. A detailed non-participant analysis of the HeSVA cohort (Hovi et al., 2007) showed no differences in perinatal, neonatal or socioeconomic variables. Lack of data on body composition in infancy and early childhood, illnesses after discharge and total duration of breastfeeding, are limitations of Studies I and II. Regarding the development of food preferences assessed in Study II, use of a nasogastric tube and more detailed analysis of the milk and types of medications used might have provided some additional information. However, these were not assessed in this study.

For assessing adult-age outcomes we used valid, exact measures as regards body composition and REE. Body composition was measured by DXA. The study participants were scanned rested, overnight-fasted, in minimal clothing and accurately positioned to achieve measures as valid as possible. REE was measured by indirect calorimetry, after an over-night fast, by trained personnel. For assessing total energy intake and food and nutrient intake in Study II we used self-reported data from a 3-day food record. Food records are designed to assess exact food intake during a certain pre-defined time period, rather than food preferences, which might affect the results. Total energy intake, however, is fairly well regulated by physiological mechanisms and thus has the least day-to-day variation. Food records are well suited for assessing the average daily energy intake. Data from food records is self-reported which may cause inaccuracy. To minimize this inaccuracy, the participants used a picture booklet for assessing portion sizes, and the forms were checked by a nutritionist.

For assessing the adult age outcomes in Studies III and IV we used validated questionnaires. It should be noted however, that we used self-applied forms, which can lead to bias due to misreporting. In Study IV, the average long-term diet of the study participants was assessed by way of a validated FFQ, which is practical in data collection and easy for participants to complete. Although diet records are more accurate in assessing the food consumed, a food frequency questionnaire provides a more useful tool for assessing the long-term diet as the day-to-day
variation in nutrient intake is large. Our forms were checked by a trained study nurse and missing items and clear errors in reporting were corrected. As the results concerning the adherence to the recommended diet were somewhat inconsistent and multiple comparisons were made, the possibility of chance findings needs to be taken in account.

In Studies III and IV we used data combined from two cohort studies from different parts of Finland. One of the main strengths is the fact that our data includes the whole range of preterm births. Owing to different cohort designs, however, there were differences in the proportions of preterm and term born groups between the ESTER and AYLS cohorts. Although the clinical examination and questionnaires used were identical in both cohorts, there is always a risk of small distinctions regarding the data collection procedures. To take these differences into account, all analyses were adjusted for the recruitment cohort. Additionally, there were some differences between the cohorts in adult characteristics. These differences were mostly present among men and were most explicit in characteristics which we have adjusted for in the analyses.

Although the participation rate in the ESTER study was relatively low, we have not found any reasons to suggest that our cohorts are not representative of the general young-adult population in Finland. Including two cohorts from different parts of the country increases the representativeness of the study sample. Power calculations for the cohorts have been performed before the data were collected. The findings of this thesis are mainly reported as mean differences with 95% confidence intervals which allow the estimation of statistical compatibility of the results.

As individuals born preterm and at term are heterogeneous in terms of other relevant variables such as size for gestational age, maternal pregnancy disorders and exposures during early infancy, we adjusted our analyses for birth size and a wide range of variables related to pregnancy. Nevertheless, this heterogeneity may matter in terms of the outcomes of our study. Given also the wide range of potential factors acting during childhood, adolescence and early adulthood and affecting the outcomes assessed in our study, lack of data on childhood growth and illnesses as well as exposures during adolescence and early adulthood should also be addressed as a limitation of this thesis.
6.6 Significance of the findings

Overweight and obesity, throughout course of life, are among the most serious public-health challenges worldwide according to the WHO (World Health Organization, 2014). Convincing evidence suggests that overweight, obesity and consequent metabolic disorders may be partially caused by programming effects during prenatal life and infancy (Hanson & Gluckman, 2011). The mechanisms acting on the background of the associations between early-life exposures and adult health have been difficult to reveal and are still mostly uncovered. The present work provides new information on the significance of early intervention in the health of those most immature at birth by focusing on those mechanisms.

The findings in the Studies I and II suggest that primary prevention of features associated with metabolic syndrome could already begin in infancy. Although the findings are not directly applicable to current care practices of preterm-born infants, as neonatal care today follows the current recommendations of much higher protein intake levels for preterm infants than the levels observed in our study, they strongly support the hypothesis that there is a link between infant feeding during the early weeks of life and long-term body composition and energy metabolism. Our results suggest that it needs to be taken into account when reducing protein intakes in infancy. The development of a healthy body composition should not be endangered by intake levels that are too low.

As the increased risk of metabolic disorders in preterm-born adults is well established, it is important to find ways of intervening appropriately. Lifestyle counselling is one of the most important of these forms of intervention. Nutritional recommendations for a healthy diet are developed according to the best available evidence, as there is a clear pathway from certain dietary habits to later disease. The present results indicate that, at least young women born early preterm have a lower adherence to current nutritional recommendations suggesting that especially those born early preterm require more detailed and comprehensive counselling on dietary habits to reduce the risk of adverse consequences in later life.

6.7 Future perspectives

Human studies carried out to examine the association between early-life exposures and health and wellbeing in later life are difficult to conduct, as the timeline of the studies is often nearly the same length as a human life span. It is very time-consuming to collect valid data on early exposures, and the duration of prospective
studies should be sufficiently long to provide adequate data on the study end points. Animal studies have been used as proxies for human studies. However, the much shorter life spans and large litters make it hard to draw meaningful and well-justified conclusions. Studies in this field are also challenging due to the confounding factors appearing during long time spans. As the associations studied are often products of genetic, lifestyle, socioeconomic and environmental factors, a wide range of confounding along the study course needs to be taken into account. Randomized controlled trials with long follow-up periods are needed for assessing the long-term effects of early nutrition. However, their use is limited due to ethical considerations. For this reason, it is important to focus on larger studies, carry out collaborative research with combined datasets and use the data derived from national-health registers in the future. Standardised protocols are also needed to be able to combine datasets and run meta-analyses of already published results.

Evidence of an association between early nutrition and body composition and energy metabolism in later life is convincing. However, human studies are scarce, mainly due to ethical reasons. Most human data is observational and may rely on close proxies. Assessing precise amounts of nutrition is also very difficult. Today, nutritional intakes in NICUs are mainly recorded electronically, which might allow less time-consuming collection of data for this patient group. However, as nutritional protocols have been developed to follow current guidelines and are fairly well harmonized, it probably is harder to find meaningful differences in relatively small study populations.

As an association between preterm birth and an increased risk of metabolic syndrome has been shown, it is important to focus research on the mechanisms behind this association. In addition, studying the factors on the causal pathway – for example lifestyle and education, and studies on biological mechanisms acting in the background would probably shed new light on this area.
7 Summary

The following results were obtained in this work:

1. Nutrition during the first three weeks of life of infants born preterm at VLBW predicts body composition and energy metabolism 20 years later. At low protein intake levels, increased protein intake is associated with a more healthy body composition. Higher intake of energy, fat and protein is independently associated with a lower relative energy intake as well as lower relative REE at an adult age. Only a part of this association is mediated by early growth.

2. Young women born early preterm have significantly fewer symptoms related to eating disorders in early adulthood when compared with their peers born at term, suggesting a lower risk of developing eating disorders in later life.

3. Young women born preterm have a slightly less healthy diet when compared with term-born peers, which may in part contribute to an increased risk of cardiometabolic disorders.

According to the results of this thesis and previous studies, primary prevention obesity and metabolic disorder should already begin during the early weeks of life. As past studies have shown an association between higher protein content in infant formula and excess weight gain in infancy, possibly resulting in increased risk of obesity later in life, the direction is toward reducing protein intakes in infancy. The results of this thesis however suggest that when doing this it is important that the development of a healthy body composition is not endangered by intake levels that are too low, especially within the most vulnerable groups of infants such as those born preterm.

As differences in diet may in part contribute to the increased cardiometabolic risk among adults born preterm, those born early preterm in particular require more detailed and comprehensive counselling on a healthy diet to reduce their risk of adverse metabolic consequences in later life.
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